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Section of Comparative Medicine

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Some Reflections on Virus Immunity

PRESIDENT'S ADDRESS

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ALL of us, I suppose, like to think that we approach the investigation of a problem with an open mind, and probably the majority of us are sufficiently unbiased to accept the hint given us by our experiments when they go counter to our preconceptions. But it does seem to me that one or two of those who have studied the question of immunity to viruses have been guilty of starting on their quest with minds made up as to what would be found. They seem to start with two assumptions. The first of these is that immunity to a bacterium is essentially the same whatever the bacterial species or its host, and the second is that the mechanism on which immunity to a virus depends is probably different. Now I should be the last to deny that immunity to the different pathogenic bacteria did not present fundamental similarities, for, of course, all these immune states depend on the interplay of the two factors, the antibodies and the phagocytic cells. None the less, differences do exist which, even though superficial, are frequently so great as largely to obscure the underlying common factors. Take, for example, the problems presented by immunity to the tubercle bacillus, the pneumococcus, and the cholera vibrio. They are so different as to constitute individual problems and of course many other examples could be given. This being so, it is surely unpardonable to launch out into a comparative study of the mechanism of immunity to bacteria and viruses with a conception of the former which might conceivably be adequate as an introduction to the subject in an elementary textbook. And it is surely equally unreasonable to expect that the manner in which the immune animal deals with a virus is likely to be the same whatever the virus. No doubt this all sounds trite and elementary; it probably is, yet it is failure to recognize these facts which has led to the making of misleading generalizations concerning virus immunity, very often with the object of showing how this differs from immunity to a bacterium.

During the last fifteen years or so we have been told in turn that active immunity to a virus could not be engendered apart from actual infection; that immunity to a virus was in part or in whole a tissue immunity; and that protective antibody had nothing really to do with the virus but was produced in response to an antigen elaborated by the tissues of the host and performed its protective rôle by uniting with the susceptible cells.

I propose this afternoon to consider with you some of these points, not with the object of discrediting them as generalizations, for that should be unnecessary, but in an attempt to find out whether or not the germ of truth lies hidden in any of these claims. May it not be that some of them at any rate, though unacceptable as generalizations, approximate to the truth when applied to some particular virus, and that,

as in the case of the bacteria, the mechanism of immunity varies from virus to virus, often to such an extent as to make of each a separate problem ?

The Necessity of Infection for the Creation of Active Immunity

When in 1924 the British Foot and Mouth Research Committee started work on the virus of this disease it was generally held that infection was essential if active immunity to a virus was to be established. So deeply rooted was this belief that when it was shown in France (Vallée, Carré, and Rinjard, 1925) and in this country (Bedson, Maitland and Burbury, 1927) that foot-and-mouth disease virus inactivated by low concentrations of formalin was capable of evoking immunity in the experimental animal, it was retorted that virus so treated was not all killed. Even though it was demonstrated that virus so treated was incapable of infecting guinea-pigs when injected in massive doses and, what is more important, could not be reactivated by serial passage in guinea-pigs, the critics were not satisfied that one was really dealing with killed virus.

A few years later, in an investigation of the virus of herpes, it was found (Bedson, 1931) that, here also, virus inactivated by means of formalin was capable of producing a solid immunity in the guinea-pig, the proof that the virus was really killed being, as before, that serial animal passage did not lead to reactivation. On this occasion, however, additional evidence of the absence of any living virus in the formolized herpes vaccine was sought. The least dose of herpes virus which—though failing to infect the guinea-pig on primary inoculation—could be demonstrated by animal passage, was ascertained, and it was shown that three injections of such a dose of living virus failed to produce immunity in guinea-pigs. Despite this demonstration doubt was still expressed in several quarters as to the possibility of immunizing with dead virus. Since then, of course, the situation has undergone a material change. The number of viruses which have been shown to immunize when injected in the dead state has been considerably augmented, and to the list can now be added the viruses of distemper, psittacosis, equine encephalomyelitis, influenza, Rift Valley fever, and rabies. Some of this new evidence has been provided by those who were outspoken critics of the earlier work ; few hesitate now to speak of killed virus when referring to non-infective but antigenically active virus.

So it would seem that the immunizing power of killed virus is no longer questioned, and you may even wonder why I have referred to this matter at such length. My reason for doing so is not to justify my earlier work but to show how this early generalization had been proved inaccurate, and to inquire as to the errors which led to its making. In my opinion, one of the main reasons, if not the principal one, for this faulty conclusion has been the inactivity of heat-killed virus vaccines. In the preparation of bacterial vaccines heat had usually been employed to kill the bacteria. The animal viruses are readily inactivated by heat and when it was found that heated virus was inert as an immunizing agent it was concluded that immunity could only be established if some at least of the virus injected was alive and could infect and multiply. Later the successful application of formalin in the preparation of antigenically active diphtheria toxoid, first of all by Glenny and later by Ramon, led to this method being applied to viruses with immediate success. Then, of course, there is the undoubted fact that some viruses, however killed, are extremely poor immunizing agents. The virus of vaccinia is a case in point, as the work of Bland (1932) and Parker and Rivers (1936) has shown.

It is clear then, and this is the point I wish to make, that no generalization on this question is possible. As in the case of bacteria, some viruses when killed have little or no immunizing power, others evoke but a low-grade immunity, whilst others again produce a solid and surprisingly durable immunity. Levinthal (1935) for instance, has succeeded in immunizing mice with formolized psittacosis virus so that

they resisted the injection of 10,000,000 m.l.d., though admittedly in this work there was no proof that all virus in the vaccines was dead, but in some of my own experiments mice vaccinated with formolized virus which could not be reactivated by mouse passage, resisted a test with 1,000 m.l.d., and this immunity was apparently unaltered 109 days after the injection of the last of three doses of vaccine, which is a considerable period in the life of the mouse. Even the generalization that heat-killed virus will not immunize may require revision in the light of the recent experiments of Fairbrother and Hoyle (1937) with heat-killed influenza virus.

Is Immunity to a Virus ever a Pure Tissue Immunity?

It is only about ten years ago that Levaditi (1926) expounded the view that the immunity to herpes virus which was engendered in the rabbit by infection did not depend on the intervention of specific antibody. He postulated some change in the infected cells which rendered them resistant to infection, a change which in some mysterious way was communicated to all susceptible cells throughout the body. And his reason for putting forward this explanation of the mechanism of immunity to experimental herpes in the rabbit, was his inability to demonstrate protective antibody in the serum of the immune animal. Had he chosen the guinea-pig as an experimental animal, he would have found, as Crawford and I did (Bedson and Crawford, 1927), that the immune state was primarily a function of neutralizing antibody.

Although this conception of Levaditi as to the mode of immunity to herpes is to-day unacceptable, I refer to it because it raises two points which I would like to consider with you. The first of these is that the mere inability to demonstrate circulating antibody is not sufficient reason for postulating a tissue immunity, and the second, arising out of the first, concerns the definition of tissue immunity.

It has been abundantly demonstrated that in the case of many viruses it is possible passively to protect the susceptible animal, and this with a dose of serum which would render the detection of antibody in the circulation of the animal highly problematical. The child of 2 or 3 years of age, for instance, can be protected against measles with 5–6 c.c. of convalescent serum; when this is dispersed throughout the body its concentration in the circulation must be extremely low, and were a suitable animal available for work with measles virus, neutralization tests would certainly fail to demonstrate antibody in this child's serum. Take another example: The guinea-pig can be passively immunized against cutaneous infection with herpes virus. As small a dose as 2 c.c. of a serum, of only moderate potency, injected intraperitoneally will protect against a considerable number of skin-infecting doses of herpes inoculated cutaneously by light scarification. Were the whole of that dose of serum retained in the circulation of the passively protected animal, the neutralization test would certainly fail to reveal it. As a matter of fact it is almost equally certain that the injected antibody, after being absorbed into the circulation, passes out again to reach the tissue spaces; if it did not it is difficult to understand how the skin could be protected against virus inoculated by light scarification. Admittedly the trauma of even light scarification will result in some outpouring of serum from adjacent vessels, but it seems to me doubtful whether the serum could arrive quickly enough and in sufficient quantity to protect the epidermal cells. In some unpublished experiments it was found that although herpes antiserum applied after scarification and before the application of virus will prevent a take, a reversal of the procedure will not prevent infection even though the interval between the application of virus and serum is as short as five minutes. Andrewes (1929[1,2]; 1930[1]) has made experiments both in the animal and in tissue culture, demonstrating the same thing, and these facts suggest that if passive protection against a virus is to be effective the specific antibody must come into close association with the susceptible cells, and to do so it would of necessity disappear largely from the general circulation.

I think this evidence demonstrates the inadvisability of assuming that absence of neutralizing antibody from the circulation means that an immune state is solely a function of the tissues. In concluding thus I know that I have the support of many virus workers and immunologists, but not everyone agrees with this point of view. In some most interesting work published recently by Traub (1936 ; 1937) concerning the mechanism of the immune state in mice and guinea-pigs to the virus of lymphocytic chorio-meningitis, the author obviously leans to the view that he is dealing with a tissue immunity. In Traub's experiments the animals were immunized with living virus which had been altered by passage through a different species—the mouse with guinea-pig virus, and the guinea-pig with mouse virus. In the protected mice neutralizing antibody could not be demonstrated in the blood, and in the guinea-pig its appearance there was irregular and did not coincide with the onset of immunity. I would prefer to think that, since neutralizing antibody did eventually appear in the blood of the immune guinea-pigs, the probability was that these animals were protected in virtue of the possession of specific antibody, but that in both species, and more particularly in the mouse, antibody production rarely proceeded far enough for it to appear in detectable quantity in the circulation.

This raises the question of what really constitutes a tissue immunity. How are we to define this state ? In his work on the mechanism of immunity to herpes virus, to which I have already made reference, Levaditi had in mind some change in the susceptible cells, which was independent of antibody, and unless we make this condition an essential part of our definition of tissue immunity, there seems little sense in using the term at all. So I would define tissue immunity as some change in the cells, independent of antibody, whereby these cells become resistant to infection.

Obviously it will be no easy matter to decide whether or not one is dealing with such a type of immunity. I have given my reasons for not accepting the absence of demonstrable circulating antibody as evidence of a tissue immunity. Nor can the rapidity of onset of immunity be accepted as unqualified evidence that the immunity is independent of antibody. Wright (1927) has shown that in the rabbit which has received an immunizing dose of killed pneumococci some immunity is evident in twenty-four hours, long before the appearance of demonstrable antibody, and in the case of the guinea-pig which has been given an injection of formolized foot-and-mouth virus, some degree of specific resistance is present in forty-eight hours (Bedson, Maitland, and Burbury, 1927). Yet from the evidence available it seems to me justifiable to conclude that, both in the immunity of the rabbit to the pneumococcus and of the guinea-pig to foot-and-mouth virus, antibody is an essential part of the mechanism, so that unless the onset of immunity were extremely rapid it would seem rash to conclude that it was independent of antibody.

Have we then any example of a true tissue immunity ? Does it ever occur ? As you know, an insusceptibility of the skin to infection with certain bacteria can be produced by local application of such substances as nutrient broth, and Ledingham (1927) has shown that the infiltration of the rabbit's skin with indian ink will engender an insusceptibility of the treated skin to vaccinia virus. Downie and McGaughey (personal communication) found that the injection of normal mouse-serum into the skin of a mouse rendered that area of skin insusceptible to a small dose of ectromelia virus injected after a lapse of a few hours ; the mouse-serum was shown to be free from specific neutralizing antibody. These changes, however, are purely local and non-specific, and although presumably due to some change in the cellular constituents of the tissues and therefore entitled to be considered as a tissue immunity, they are not examples of the kind of thing I have in mind when speaking of tissue immunity.

It seems to me that R. N. Salaman's experiments with the X virus of potato are of the nature of a true tissue immunity (1933). By selection Salaman obtained two strains of X virus, one practically devoid of pathogenicity, the other causing a severe disease. Plants inoculated with the former strain were found to be insusceptible

to infection with virulent X virus; the protection was specific. Evidence of the same sort of thing in the case of other plant viruses has since been demonstrated by other workers, and since in plants there is no evidence of humoral immunity it would seem that the explanation of this phenomenon is that once the plant-cells are infected with the strain of low pathogenicity they are insusceptible to reinfection with the closely related virulent strain of the same virus.

Of course conditions in the plant are so different from those in the animal that the occurrence of a tissue immunity in plants might have little interest for us, were it not that a very similar phenomenon has come to light in the case of an animal virus; I refer to the so-called interference phenomenon observed by Hoskins (1935) with strains of yellow-fever virus, and studied more intensively by Findlay and MacCallum (1937). These investigations have shown us that neurotropic yellow-fever virus protects against pantropic strains of this virus; monkeys, for example, inoculated intraperitoneally or subcutaneously with mixtures of neurotropic and pantropic yellow-fever virus, survive, whereas the same dose of the pantropic strain almost invariably proves fatal. Even when the injection of the neurotropic virus followed that of the pantropic strain at an interval of as much as twenty hours, some protection was obtained (Hoskins, 1935), and this fact, together with the inability of Findlay and MacCallum to demonstrate any precocious production of neutralizing antibody by neurotropic yellow-fever virus, seems to rule out the possibility of antibody entering into this phenomenon. As Findlay and MacCallum suggest, the explanation would appear to be that cells already occupied by actively multiplying virus cannot be reinfected. The fact that the protection afforded by neurotropic against pantropic yellow-fever virus was extended to an immunologically unrelated virus, that of Rift Valley fever, which, however, affects similar cells to those attacked by yellow fever, supports their argument.

This seems to be an example of what might be termed a tissue immunity in the strict sense of the term, but it is the only one which, to my mind, seems to bear the stamp of the genuine article. Even the immunity to the virus of poliomyelitis, about which there is much discussion to-day, I would still hesitate to accept as an example of a true tissue immunity. I must admit, though, that I am far from clear in my own mind as to what exactly is the mechanism of this immunity. The recent observations of Brodie, Fischer, and Stillermann (1937) demonstrate that the correlation between the development of neutralizing antibody and apparent infection is by no means a close one. Convalescents from poliomyelitis may possess little or no antibody in their blood; when infection occurs in an individual already possessing antibody there may be no increase in its titre. Facts such as these, however, might be explained by assuming that the antibody which appeared in the circulation was a response to virus which reached tissues other than those of the central nervous system, and that in infections with this highly specialized neurotropic virus the amount of virus which generalized was an extremely variable quantity. And if our conception as to the route followed by this virus when it infects, is correct, then it would seem improbable that circulating antibody could play any serious part in ensuring protection against poliomyelitis. The experiments of Schultz and Gebhardt (1935), in fact, show that this is probably a correct deduction; monkeys passively immunized, and possessing as much neutralizing antibody in the circulation as convalescent animals, were found to be almost as susceptible to infection by the nasal route as the normal animal. Active immunity to poliomyelitis virus would appear to be engendered alone by infection.

Does this mean that the susceptible cells of the central nervous system are capable of producing specific antibody and that only when infection takes place is the stimulus to this local production of antibody forthcoming? And if this is so, how does this antibody do its work? Where does it lie in wait for the invading virus? Or, on the other hand, are we dealing with an immunity of the neurons which is independent of

antibody—an insusceptibility determined possibly by persistence of virus, something akin to the interference phenomenon ?

For the moment the available evidence does not enable one to say which of these hypotheses is the correct one. There is also the question raised by Jungeblut (1936) as to whether insusceptibility to infection with poliomyelitis virus may not sometimes be dependent on physiological factors such as the secretion of endocrine glands or vitamin intake. Much remains to be done before a clear understanding of this interesting problem is obtained.

Mode of Action of Neutralizing Antibody

It would appear then that although immunity to an animal virus may sometimes be of the nature of a tissue immunity, this is probably a rare occurrence, and that in the vast majority of cases, at any rate, antibody is the all-important factor in the immune state. The question then arises as to how this antibody works.

I should like, first of all, to say a word about the thesis of Sabin (1935). He claimed that union between virus and neutralizing antibody did not occur—he doubted even whether its corresponding antigen was a constituent of the virus—and he expressed the view that the function of the antibody was to unite with the susceptible cells and so to protect them from infection. Already when Sabin published his findings evidence was available to show that in the case of two viruses, herpes (Wilson Smith, 1930 ; Bedson, 1928), and vaccinia (Andrewes, 1930[2]), virus and neutralizing antibody did unite *in vitro*, though admittedly in the case of vaccinia virus this union was slow in taking place. Some of this evidence Sabin chose to ignore. Since the publication of his papers further evidence has appeared to controvert his thesis. Burnet (1936), Magill and Francis (1937), have both demonstrated that influenza virus and neutralizing antibody do definitely unite. M. H. Salaman's (1937) carefully controlled experiments with vaccinia virus have left no doubt that the antigen responsible for neutralizing antibody is a part of the virus and that in suitably balanced mixtures of virus and antiserum the neutralizing antibody is fixed by the virus and is removed when the virus is centrifuged out. The fault in Sabin's work is not that he failed correctly to observe the facts, but that the plan of his experiments did not allow of the correct answer being given. This emerges clearly from the recent paper of Enders and Schaffer (1937), where it is shown that all Sabin's findings can be paralleled with a Type III pneumococcus and its antiserum. Sabin would surely have hesitated to draw the conclusions he did had he been working with a bacterium instead of a virus, yet his facts might have been the same.

It would seem then that when one makes a mixture of virus and specific serum in suitable proportions, neutralizing antibody and virus unite, though I think there is little doubt that this union is not a firm one, at any rate at first. There is also evidence that on introduction into the animal body dissociation of such a virus-antibody complex takes place. This was shown, for instance, by the experiments of Craigie and Tulloch (1931) with vaccinia virus. Suspensions of vaccinia virus and anti-vaccinial serum were made at optimum proportions previously determined by flocculation experiments. These mixtures were centrifuged and the deposit was dried, with or without previous washing. Such a dried deposit when resuspended in saline and injected intradermally in rabbits produced no lesion ; inoculated subcutaneously it immunized. The deposit therefore contained both virus and neutralizing antibody, which must have united with the virus, since it came down with it, and this virus and antibody complex could be dissociated *in vivo*, as was shown by the fact that injection into the testicle gave rise to frank infection.

In the neutralization tests as usually carried out in virus work the mixture is tested for neutrality, often long before union between virus and antibody could have taken place, and the neutrality of the mixture depends on the injected dose possessing

an adequate amount of antibody. What constitutes an adequate amount of antibody depends on the virus, the route of inoculation chosen, the rate of absorption from the site of injection, and the number of susceptible cells in its immediate neighbourhood. The dilution phenomenon is a question of the size of dose, as Findlay (1936) has pointed out. A mixture of psittacosis virus and antiserum injected intraperitoneally in mice, in a dose of 0·5 c.c., will appear neutral, whereas 0·1 c.c. of the same mixture by the same route produces infection. The so-called neutralization test is a test of the ability to produce passive protection, and in the case of some viruses, at any rate, under cover of this passive protection an inapparent infection is set up. With psittacosis virus, for instance, this is readily demonstrated, for in mice which have supported an injection of virus and antiserum without apparent illness I have had no difficulty in demonstrating active virus in the spleen even three months later. And the amount of virus to be found in this organ is so great, sometimes even discernible by direct examination of spleen smears with the microscope, that one is left in no doubt that the injected virus has multiplied to a considerable extent, yet no symptoms of illness have ensued.

So the effect of neutralizing antibody on the virus, even when union has taken place, does not result in death of the virus; indeed, from what one knows of the action of bacterial antibody *in vitro*; I should have been surprised if viricidal antibody had been found to have any lethal effect by itself. Whether as the result of prolonged contact with neutralizing antibody the virus is gradually inactivated, it is impossible to say, since there is no evidence available on this point, nor do we know whether complement might aid in bringing about virus destruction. We do know, however, that in the case of some viruses the immune animal may have virus and antibody in the blood even some time after the onset of immunity. This can be shown in the case of psittacosis virus, and Downie and McGaughey (1935) have found that mice immune to ectromelia and possessing a considerable amount of neutralizing antibody in their serum might also have virus in their blood; in the latter case the presence of virus was completely masked by the antibody. So it would seem that if virus is killed *in vivo* by neutralizing antibody, possibly with the aid of complement, the process is a slow one and cannot by itself explain the immunity conferred by antibody.

Is the function of antibody then to prepare the virus for phagocytosis and intracellular destruction? Here again we have not the evidence on which a definite answer can be based. We know from the experiments of Andrewes (1929[2]; 1930[1]) in this country, and of Rivers and Haagen and Muckenfuss (1929) in America, that in tissue culture the addition of immune serum to the cultures before the virus, prevents infection of the cells; under these conditions virus does not multiply and inclusion bodies are not formed within the cells. This might mean either that the antibody prevented the virus entering the cell in which it would find the environment essential to its multiplication, or that it so altered the virus that on reaching the interior of the cell it was destroyed. This is no easy matter to settle. Downie and McGaughey (1935) found that in tissue culture experiments with ectromelia virus, antibody, even when added to the tissue before the virus, only inhibited multiplication of virus during the first few days of incubation; in such cultures growth of virus always occurred if the period of incubation was prolonged to 8–12 days. This finding might be interpreted as indicating that inactivation of virus sensitized by antibody took place inside the cells and that the delay in growth was due to an incomplete destruction of virus, leaving a small residuum of active virus which required some time in which to grow out and reveal its presence. On the other hand it might merely mean that as the result of prolonged incubation the tissue cells had lost some of their initial vitality with the result that the cell membrane no longer presented such an efficient surface with which to hold the virus-antibody complex. Some virus might thus be enabled to free itself and penetrate a cell which, however, was still sufficiently unchanged to support virus growth. In support of the former explanation is the work of Smith

(1929), Douglas and Smith (1930), and Fairbrother (1933) with vaccinia virus, and Jamuni and Holden (1934) with herpes, showing that the addition of leucocytes to a virus-antiserum mixture increases the neutralizing effect of the antibody and carrying with it the suggestion that the function of antibody is to prepare the virus for phagocytosis and destruction within the cell. The fact of the matter is that, owing to the small size of even the larger viruses and the difficulty of staining them, it has not been possible to obtain direct evidence on this point and so settle the question as to whether the function of antibody is to hold virus at the surface of the cells where it might slowly be killed, possibly with the aid of complement, or whether it promotes phagocytosis of the virus with subsequent intracellular destruction. It does seem to me, however, that with a large virus like psittacosis, capable of being stained differentially by a method like that of Castañeda, it should be possible to carry out phagocytic experiments ; only the lack of success encountered in the preparation of a really potent antiserum to this virus has kept me from attempting this type of experiment.

Persistence of Virus after Recovery from Infection

It would seem, then, that the antibody in the tissue spaces lies in wait, as it were, for the virus, and uniting with the virus, either prevents it getting inside the cells or prepares it for intracellular destruction. But whichever of the two mechanisms it employs, it is clear that the protection it affords is not always complete. Some virus may escape destruction ; a cell or two is infected, virus multiplies, and the cells break down, with the liberation of more virus. Again a small quantity of virus escapes the attention of the antibody, a few fresh cells are infected, and in this way persistent infection is established, providing that continued antigenic stimulus which maintains antibody at a level sufficient to prevent the infection assuming clinical proportions.

This raises the question as to how commonly recovery from natural virus infections is associated with a persistence of that infection, or in other words, in the setting-up of the carrier state. The solid and durable immunity which is left by so many virus diseases suggested already, some years ago, that recovery was possibly not as complete as it appeared to be, and that somewhere in the tissues of the host the infecting virus persisted. The lifelong duration of the immunity, which is a feature of quite a number of these virus infections, is difficult to explain except on the basis of a continuous or frequently repeated antigenic stimulus. It is true, of course, that in the case of the durable immunity to a disease like measles it is not necessary to postulate persistence of infection. The recovered individual, at any rate in the large communities of our modern civilization, would be exposed to repeated reinfection and in this way the initial immunity could be maintained at an adequate level ; the state of affairs might be the same as in diphtheria for example. But in some virus diseases such an explanation of the duration of immunity hardly suffices. An individual who has recovered from an attack of yellow fever, for instance, may have quite a high titre of neutralizing antibody in the blood years after recovery and yet may not have been exposed to reinfection. And a study of animals which have recovered from experimental infection with a number of viruses has shown, in fact, that the persistence of infection is by no means uncommon and in the case of some viruses almost the rule. Olitsky and Long (1929) have shown that in the rabbit which has recovered from infection with vaccinia the virus can be found in the tissues 133 days after infection, and in monkeys which had survived an attack of poliomyelitis Olitsky, Rhoads, and Long (1929) were able to demonstrate active virus in the central nervous system 23 days after recovery. In both cases direct inoculation of the tissues into susceptible animals was without effect, the virus being masked by the presence of neutralizing antibody ; only when the tissue suspensions were submitted to electrophoresis were virus and antibody separated and the persistence of infection revealed.

In the case of psittacosis the demonstration of virus in the immune animal is a simple matter, since the amount of specific antibody in the blood and tissues is so small that direct inoculation of a suspension of the tissues from the recovered animal rarely fails to reveal any active virus present. And in some cases the virus may be present in the tissues in such quantity that microscopic examination of smear preparations is all that is necessary to demonstrate it. I have already referred to the infection that can be set up in mice which have been inoculated with an apparently innocuous mixture of psittacosis virus and antiserum ; in this case an abundance of virus was found three months after inoculation. In another experiment which I made, mice were first immunized with formalin-killed virus and then injected intraperitoneally with a small dose of active virus, between 100 and 1,000 m.l.d. The mice remained perfectly well and were killed, two at a time, to be examined for the presence of virus at intervals of three, five, seven, and nine months after the test inoculation. Since it is in the spleen that this virus multiplies principally after intraperitoneal inoculation, it was in this tissue that virus was sought both by direct microscopic examination and by injection into normal mice. Only in the two mice killed nine months after inoculation did I fail to find virus, and the virulence of the spleen suspensions of the seven-month mice did not appear to be inferior to that of those made from mice killed earlier. Thus the immunity of these mice which had received the formol vaccine was by no means complete, since the test inoculation set up an inapparent infection which in this experiment ran a course of between seven and nine months.

That the virus does actually multiply in vaccinated mice was shown in another experiment. In this case mice which had been immunized with formolized virus were injected intraperitoneally with between 100 and 1,000 m.l.d. of virus, a number of normal mice receiving the same amount. At intervals of two, four, and seven days after inoculation an animal in each group was killed and the amount of virus in the spleen titrated and the heart's blood examined for virus. By the seventh day the control mice were moribund and contained an abundance of virus both in spleen and circulation. The vaccinated mice had remained apparently well, but virus had increased progressively up to the seventh day, and though less in amount than in the control mice at that time, it was yet in sufficient quantity to be readily found in spleen smears with the microscope and was even present in the blood-stream. Whether the absence of symptoms produced by the infection in these immune mice is due solely to the fact that multiplication is kept within moderate limits or is dependent on other factors requires further investigation ; sufficient has been said, however, to show that with psittacosis virus, as with some other viruses, persistent infection in the immune state is readily demonstrated.

How common this state of things is in virus infections remains to be seen, but the solid immunity which follows recovery from so many virus infections, and the intracellular habit of growth of these agents, would suggest that it is by no means unusual. In saying this I do not wish it to be thought that I consider this phenomenon of persistent infection to be in any way a monopoly of viruses, because of course we know that the same sort of thing occurs in the case of both bacteria and protozoa, but the intracellular mode of existence of viruses would seem to make it peculiarly difficult for the host to free itself completely from the invader after recovery. And the importance of this phenomenon is not solely concerned with the explanation of the solid immunity which so many virus infections leave behind them. It must play a very considerable part in the epidemiology of virus diseases and it has a very definite bearing on the methods which we use for the purpose of prophylactic immunization. These, however, are questions which I can do no more than mention this afternoon.

In this survey of some aspects of virus immunity which I have given you, and of whose shortcomings I am acutely aware, I have tried to show that, despite a fundamental similarity which is to be found in the mechanism of immunity to viruses—

a similarity which extends to bacterial immunity—differences exist which, though superficial, are often so great as to make it illusory to talk of virus immunity as though it all conformed to a common pattern. The problem of immunity to any given virus or bacterium is a problem to itself; each has its special features and peculiarities. And it seems to me that those who attempt to generalize about virus immunity, making some picture which is supposed to be applicable to any virus and then proceeding to compare this with what pertains in bacterial immunity, are out of touch with reality.

I know, of course, that few will find themselves in complete agreement with all that I have said; indeed it would be extraordinary were it not so, since what I have been attempting to give you merely represents my own personal interpretation of the evidence. There must be many points that some of you would like to discuss, conclusions that you would dispute. Perhaps it is well for me that my privileged position this afternoon relieves me of the necessity of defending myself in open debate; the onslaught might be overwhelming.

Nevertheless I believe that the majority will approve my major thesis, though some will conclude that I have fallen into that error which I have been at such pains to condemn—the closed mind.

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Section for the Study of Disease in Children

President—T. TWISTINGTON HIGGINS, O.B.E., F.R.C.S.

[*October* 22, 1937]

Familial Ectodermal Defect.—R. T. BRAIN, M.D.

L. S., female, aged 12, apparently normal at birth. When about 6 years old had bronchopneumonia, followed by whooping-cough, after which practically all her hair fell out. New hair soon began to grow, but a general defluvium continued and her comb always collects much hair. Her skin is not abnormally dry, and she does not complain of the heat. Her first teeth appeared at 9 months of age and they were pointed from their first appearance. General health good. Intelligence normal.

Family history.—Father has one dystrophic nail which incompletely covers the nail bed; his hair and teeth are said to be normal. The mother has no defects of hair, nails, or teeth; her eyes are brown and normal. She is not blood-related to her husband. A son, R., aged 14, has normal hair, but his skin is unusually dry, and he complains of the heat in summer and cannot tolerate many bedclothes. He had his first teeth at 5 months. All his teeth are widely separated and are definitely peg-shaped. Evidently he had only eight in the lower jaw and ten in the upper jaw, of which only five in the upper jaw remain. No permanent teeth have shown signs of appearing, and it was stated that none were seen on X-ray examination. His nails are thin and dystrophic, some being slightly spoon-shaped, others being slightly separated at their terminal portion from the nail-bed, and one on the left index finger occupying only half the normal bed. Another son, aged 20, and twin girls aged 3, have no similar defects, and are apparently normal.

On examination.—A bright, well-developed girl, with blue eyes and pale, straw-coloured hair. Her hair, 4 to 5 in. maximum length, is fine, silky, and wavy, and it stands out rather like a wig. Microscopical examination shows absence of pigment, and considerable variation in diameters of various hairs, but individual hairs are uniform and show no nodes or tendency to fracture. The upper incisors have been removed; the lower incisors are round, thin, conical pegs, and the canines are very similar; the molars are better shaped, but small. The superior maxilla appears to be undeveloped, allowing the upper lip to fall in, but the lips are not thickened, although the cheeks are also rather sunken. The nails show some dystrophy, the right index nail occupying half the nail-bed, and the right little finger-nail being partly separated.

These cases are good examples of minor ectodermal defect, and illustrate the familial tendency, but no other cases in the families were known. Dr. Cockayne's

excellent book on " Inherited Abnormalities of the Skin " describes similar dystrophies, and dermatologists are indebted to him for much enlightenment on this group of rare anomalies.

Dr. E. A. COCKAYNE said he had no doubt that the children in cases of this kind suffered from a mild form of anidrotic ectodermal dysplasia. He had pointed out that, although in most families this was inherited as a sex-linked recessive, it was partially dominant in others. Recently, Levit (1936) had stated that is was always sex-linked, but was incompletely recessive or conditionally dominant in some families, so that heterozygous females might have the dysplasia. though usually in a milder form than males. This explanation would apply to most families, in which there was direct descent. If, however, the pedigree published by Battersby (1936) was correct, there was descent from father to son, which could not occur with a sex-linked character, recessive or dominant. In that family, therefore, it was autosomal and conditionally dominant. In the family shown to-day the father had one nail defective, like his children, and, if this was to be regarded as a manifestation of the dysplasia, it must be autosomal in this family also.

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Multiple Pyæmic Abscesses in Scarlet Fever: Operations: Recovery.—J. D. ROLLESTON, M.D., and PHILIP TURNER, M.S.

May 11, 1936: A boy aged 5½ years was admitted to the Western Fever Hospital with an apparently mild attack of scarlet fever, on the third day of disease. The temperature was normal on admission but rose to 100·4° two days later when 40 c.c. of anti-scarlatinal serum was given, and for the next seven weeks showed a partly remittent and partly intermittent course. Left otorrhœa developed on May 15. From May 19 to August 1 the following complications occurred:—

May 19: Osteomyelitis of left ulna. May 24: Osteomyelitis of right scapula. May 27: Suppurative arthritis of both ankles and right elbow-joint. June 1: Suppuration of right knee-joint. June 23: Subcutaneous abscess over sacrum. July 9: Abscess of right thigh.

All the wounds were healed by August 12, when he was first allowed up, but he was unable to walk by himself until September 15 and the otorrhœa persisted until a week before his discharge on September 30, 1936.

After his discharge he was treated at St. Mary Abbots Hospital by massage and passive movements. For a long time there was considerable limitation of the movement of the affected joints and it was not until the summer of 1937 that he recovered complete movement of his right ankle; all the movements are now perfect.

Mr. PHILIP TURNER: There are several points of surgical interest about this case. In the first place for about two weeks after the first appearance of a pyæmic abscess, the boy was so gravely ill that the chance of recovery appeared to be very slight. In the second place, though recovery with no impairment of movement after drainage of pyæmic joints in children is not uncommon, it is most unusual for recovery, without any deformity or disability, to occur after so many joints and bone have been infected. Four major joints were involved, the right knee, the right elbow and both ankles: In two of these, the right ankle and the right elbow, a rubber drainage tube had to be inserted right through the joints which appeared to be quite disorganized. Movements in all these joints are now perfect though at first there was stiffness of the right ankle, with drop-foot, which, however, completely disappeared after a long course of massage and passive movements. The large abscess in the upper part of the right thigh was at first thought to be due to osteomyelitis of the femur, but at the operation it was found that the pus was tracking downwards through the sacro-sciatic foramen. This, together with the subsequent appearance of abscesses over

the sacrum, suggests that there was a septic focus somewhere in that bone. All these abscesses healed after drainage without the separation of a sequestrum.

Cœliac Disease with a Conditioned Vitamin Deficiency resembling, but not typical of Pellagra.—REGINALD LIGHTWOOD, M.D., and VICTORIA SMALLPEICE, M.D.

B. S., male, aged 15 months, the second child of a healthy family living in excellent surroundings. Birth-weight 6 lb. 12 oz. Breast-fed six months and has since had marmite, halibut oil or radiostoleum, and orange juice continuously.

Well till 5 months, when he developed a rash on the trunk which spread to the limbs and persisted. At 6 months attended out-patient department (Radcliffe Infirmary, Oxford) on account of seborrhœic eczema, and was admitted at 8½ months as weight had fallen from 15 lb. 14 oz. at 6½ months to 12 lb. 14 oz. In-patient two months, during which time he developed measles. Investigations said to have included lumbar puncture, barium meal, and X-ray examination for rickets—all proving negative.

Condition on examination 19.6.37.—11 months. Weight 14 lb. 1 oz.; very small; irritable; frowning but no true photophobia (fig. 1); high colour; dry eczematous

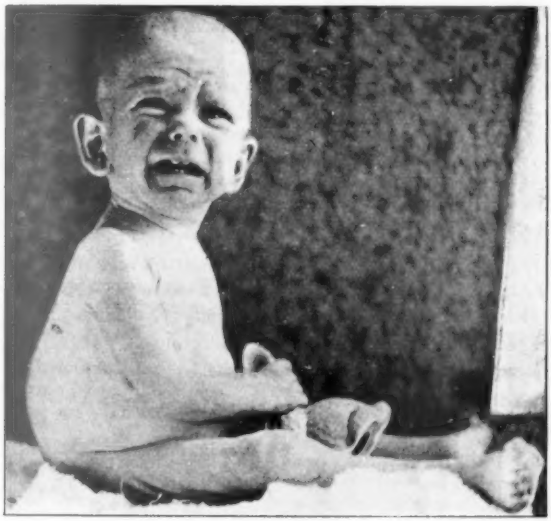

FIG. 1.

skin. Marked hypotonia with kyphosis; wasting (figs. 2 and 3), especially of buttocks; hands and feet large in comparison with limbs; fingers sausage-shaped and bluish-red in colour. Abdomen very large. Knee-jerks obtained with difficulty. Has never crawled or been able to raise himself to sitting position. Mother notices that arms very quickly get tired and he resents having his hands touched. Dislikes his food. Motions recently large and offensive, two daily. During the last three weeks corneal changes have been noticed.

FIG. 2.

FIG. 3.

Investigations

X-ray (Dr. Shires, 21.6.37).—*Wrists and hands:* No bone changes.

Wassermann reaction: Negative (mother and child).

Urine: Faint trace of albumin on one occasion; subsequently no albumin, no sugar.

Stool analysis (expressed as % of dried fæces):

	19.6.37	*3.7.37*	*10.9.37**
Split fat	20·87	40·5	12·5
Unsplit (neutral)	1·78	2·0	19·2
Total fat	22·65	42·5	31·7
Percentage of fæcal fat (split) ...	92·1	95·3	39·4
Percentage of fæcal fat (unsplit) ...	7·9	4·7	60·6
Microscopic	Nil		

*Whilst on low fat diet.

Progress and treatment 9.7.37.—Nine days' treatment with 5 c.c. concentrated vitamin B_1 extract twice daily, kindly supplied by Professor Peters. Skin showed improvement but appetite unchanged and weight continued to fall.

16.7.37: Low fat diet. Gain of 14 oz. in first two weeks, but this was not maintained. At this time he was not seen regularly.

4.10.37 : Was back on normal diet. Face is beefy red and shows some scaling. Legs : Areas previously sunburnt have become raised, red, and scaly since this date. Is taking marmite, halibut oil and fruit juice.

Ophthalmologist's report : Mr. J. H. Doggart described the corneal condition as follows : "There is a horizontal, band-shaped opacity of the corneæ due to hyaline degeneration of the interpalpable region."

Vitamin supply has been provided for as follows : (1) Orange-juice daily since weaning at six months ; (2) ryzamine B, ♏i, daily for the past two months ; (3) radiostoleum, ♏iii, daily for the past three and a half months ; previously, halibut oil, ♏iii daily.

The clinical picture presented by this patient is very unusual. At first glance, pink disease might be suspected, but on closer examination the distribution of the rash and its colour are seen to be not at all like that of pink disease. Further, the condition has been getting gradually worse for ten months, a much longer course than that usual in pink disease. Again, the infant has not been noticeably sweaty or shown sustained tachycardia.

In some respects, the skin lesions suggest pellagra but are not typical, and it is difficult to see how such a deficiency could have arisen, unless it be a "conditioned" vitamin-B deficiency. If the suggested diagnosis of cœliac disease is correct, this might have brought about such a "conditioned" deficiency by interfering with intestinal absorption. It is possible that the condition of the corneæ may be due to vitamin-A lack, though again, the appearance is not characteristic.

Discussion.—Dr. R. C. JEWESBURY said he would like to have more information about the diet and the character of the stools. What was the amount of total fat and split fat? He thought the case resembled one of vitamin deficiency but he admitted that the exact diagnosis was very difficult.

Dr. H. S. STANNUS said he thought the condition was not pellagrous ; the history and the dermal manifestations hardly fitted in with that disease. It would be interesting to determine the intravenous glucose curve by Ross' method. Exhibition of a crude liver extract, such as campolon, might be well worth while quite apart from any reticulocytosis produced.

Dr. RICHARD HAMBURGER : In the abnormal stools of cœliac disease rapid passage of intestinal contents is confined principally to the small intestines (R. Freise). In consequence of the short stay of intestinal contents in the small intestines, the digestive process normally carried out by this viscus is imperfect. This deterioration of the digestive process offers a reasonable explanation for the unsatisfactory utilization of certain foodstuffs in general and in particular of the vitamin administration in this case. The disproportionate rate of peristalsis may be tested by barium meals. Where this mechanism is present tincture of opium materially helps digestion and absorption by slowing down the movement of the small intestines.

Dr. PEARSE WILLIAMS said that the distribution of the rash was noteworthy ; it was limited to the exposed parts of the limbs and the face. On first inspection the condition much resembled that seen in pink disease. It was probably an allied nutritional disorder. He also suggested liver extract as an addition to the increased dosage of vitamins which had been recommended.

Dr. VERNON BRAITHWAITE agreed that though the patient presented some symptoms resembling pink disease that condition was not really present. He suggested that the child was suffering from physical allergy to light or heat—as described by Dukes. The skin lesions all occurred on the exposed parts, and the therapeutic test of keeping the child in subdued light and a cool atmosphere would be worth a trial.

POSTSCRIPT (13.11.37).—From October 25, campolon ½ c.c. intramuscularly twice weekly, and tincture of opium ♏i with kaolin twice daily, have been given. The weight (previously stationary) has increased by more than 2 lb. and the skin lesions have begun to recede.—[R.L.]

Two Cases illustrating the use of Intravenous Glucose Curves to Test Liver Function.—REGINALD WILSON, M.D. (for Dr. E. A. COCKAYNE, and Dr. DONALD PATERSON).

I.—Thomas C., aged 8 years, admitted to the Hospital for Sick Children in June 1937, on account of jaundice and a slightly enlarged liver.

Laboratory findings.—Urine: Bile pigments present. Stool: Bile pigments absent, Van den Bergh reaction: Direct, positive biphasic; indirect, 7 units. Plasma phosphatase 51 units (normal 5 to 15).

There was a rapid clinical recovery but the plasma phosphatase remained high (35 units) after the Van den Bergh reaction had become normal. Readmitted one and a half months after discharge, with an exactly similar attack. Plasma phosphatase then 43 units. After a similar clinical recovery had taken place, oral lævulose tolerance showed no impairment of function. Intravenous glucose curves (Ross technique) showed gross impairment; the curves were improved after an injection of liver extract (campolon) intravenously. Plasma phosphatase now 19 units.

II.—Doris S., aged 8 years, admitted on account of malaise, anorexia and frequent nose-bleeding.

On examination.—Moderate pallor; large liver and spleen; dilated superficial venules on the face.

Laboratory findings.—Blood-count: R.B.C. 4,400,000; W.B.C. 5,200; Hb. 72%; C.I. 0·8. *Differential:* Polys. 24%; lymphos. 67%; monos. 7%; reticulocytes 3·2%. Platelets normal. Urine sterile. Wassermann reaction negative. Fragility of R.B.C. normal. Van den Bergh reaction: Less than 0·5 units. Sedimentation rate: 12 m.m. at one hour.

An intravenous glucose tolerance curve showed definite impairment of function which was markedly improved after a dose of liver extract intravenously (campolon 2 c.c.). A liver biopsy showed a round-celled infiltration confined to the portal radicles.

Discussion.—Dr. W. W. PAYNE said that he had for some time been interested in the plasma phosphatase in catarrhal jaundice. He had found that—unlike what occurred in the adult in this condition—in the child the phosphatase rose to quite high values. It returned to normal after the Van den Bergh reaction had done so. In the first of these two cases it was noteworthy that the phosphatase did not return to normal after the first attack, but remained persistently raised. This was so unexpected that estimations were made at intervals after he had left the hospital, in order to find out what happened, but the level continued to be raised. After the second attack of jaundice the phosphatase returned nearer to the normal level, but no normal value had yet been obtained. The high phosphatase appeared to indicate some persistent hepatitis which had not yet completely cleared up.

Cretinism (untreated) with Bone Changes simulating Osteochondritis (Perthe's Disease of Hip).—R. C. JEWESBURY, M.D.

P. D., female, aged 8 years 9 months. Complaint: "Small stature."

Previous history.—Born at term. Normal labour. Birth-weight 8¼ lb. Breast-fed 9 months, then given normal diet. Health good; had varicella and pertussis. Mother states that the child made normal progress until 3 years of age when she had a fall, scalding herself and knocking her head (did not become unconscious). Since then she ceased to talk until 5 years of age, when she began to speak again. Mother also states that she has not grown in size or intelligence for the past three years.

Family history.—Father: height about 6 feet. Mother: height about 5 ft. 9 in. Both well. Brother aged 15, a well-built lad. Skiagrams of mother and brother show normal epiphyses.

Present condition.—Temperature, pulse, and respiration normal.

Measurements: Height 41 in. Weight 45½ lb. Span 39 in. (48 in.). Circumference of head 22 in. (20¼ in.), chest 23 in. (23½ in.), abdomen 23½ in. (20¾ in.). Height: Vertex to pubis 20¼ in. (24 to 25 in.); pubis to soles 20¾ in. (24 in.). (Figures in brackets are the normal measurements.)

Short plump child. Skin sallow but not coarse. Hair dry, coarse, slightly brittle. Eyebrows normal. No axillary or pubic hair. Head large; lower part of face looks unduly large. Bridge of nose slightly sunken. Teeth small, hypoplastic and carious. Tongue not enlarged. Hands short and rather stumpy, puffy over dorsum. Abdomen prominent; fat abdominal wall; no hernia. Stands with lordosis. No goitre. Neck short. Limbs short but not achondroplasic. Mentally young for her age; "slow in the uptake". Heart, lungs, throat, ears, central nervous system, urine: Normal.

Investigations.—Skiagrams of bones show changes of osteochondro-dystrophy. Sella turcica is unusually large. Retarded epiphyses. Wassermann reaction negative. Blood urea 28 mgm.%. Urea concentration test 3%+ all specimens. Blood calcium 9·3 mgm.%. Blood-count: R.B.C. 4,080,000; Hb. 82%; W.B.C. 5,800. Normal differential. Basal metabolic rate 36%.

Dr. LIGHTWOOD said that the radiological appearances in the femoral heads closely resembled those of Perthe's disease and were to be regarded as characteristic of cretinism (especially cretins untreated and past the age of infancy) and also of young persons with myxœdema. He believed that Professor Snapper of Amsterdam had been first to draw attention to this point, and he (Dr. Lightwood) had himself been able to confirm it on several occasions since he had become aware of Snapper's observations.

POSTSCRIPT (18.11.37).—Since the child has been under observation it has become apparent that all the abnormalities in her condition, including the X-ray findings, can be attributed to hypothyroidism, but at first X-ray appearance of the hip-joint suggested Perthe's disease.—[R.C.J.]

Pathological Specimen from a Case of Jaundice (shown February 28, 1936).[1]—R. C. JEWESBURY, M.D.

Betty R. Attacks of jaundice of obstructive type (urine dark, stools light), starting at the age of 5. The attacks were preceded by malaise and abdominal pain.

First observed when aged 8 (1935) when she was slightly undersized. The liver was just palpable and the spleen hard and down to the umbilicus.

Investigations.—Van den Bergh: Direct positive. Icterus index 25. R.B.C. 3,811,000; Hb. 90%; W.B.C. 6,000. Normal differential count. Fragility: Less than 0·4% sodium chloride. Platelets 220,000.

Three months later the liver was larger, with a rounded and irregular edge. Bile persisted in the urine. There was a more or less persistent jaundice with exacerbations.

Fasting blood-sugar 0·077, with a normal blood-sugar curve. Wassermann negative on three occasions; in five siblings and the parents also negative.

Again observed at the end of 1936 when aged 9, with two weeks' history of enlargement of the abdomen. Thin and wasted. Mild icterus. Marked ascites; ascitic fluid showed lymphocytes +++ and was sterile on culture. Wassermann reaction negative. The ascites responded well to novurit.

Returned in May 1937 with ascites which failed to respond to novurit but yielded to urea. The spleen remained *in statu quo* but the liver could only be felt with difficulty.

Readmitted in July with hæmatemesis. Ascites was marked and failed to respond to diuretics. Paracentesis abdominis was performed five times. The spleen was

[1] See *Proceedings*, 1936, **29**, 737 (Sect. Dis. in Child., 25).

rather swollen and the liver no longer palpable. The child became progressively more jaundiced and died.

Post-mortem examination.—The liver was small and showed an irregular surface composed of small projections. The spleen was large and tough. Varices were visible at the lower end of the œsophagus.

Specimen.—Macroscopically: The liver is much reduced in size; surface irregular; very hard on section. Appearance of a multilobular cirrhosis.

Microscopically: The section shows large areas of new connective tissue, for the most part of multilobular distribution. In this new connective tissue are numerous small blood-vessels and infiltration of round cells; also in places there are large numbers of the so-called bile-ducts. In addition the section shows the presence of bile in the small canaliculi and in the liver cells.

Section of Dermatology

President—H. HALDIN-DAVIS, F.R.C.S.

[*October* 21, 1937]

Linear Dermatosis.—GODFREY BAMBER, M.D.

S. S., a girl aged 15.

History.—Changes were noticed first on the little toe, eight years ago. Within three years the lesions had reached their present extent and have since remained unchanged.

Present condition.—On the inner side of the right buttock is a red, slightly scaly, patch almost the size of the palm. From here a narrow band extends down the back of the thigh and calf, and along the outer side of the dorsum of the foot to the little toe. The general appearance of the thinner lesions is psoriasiform, but in places along the band the horny layer is much thicker and over the tendo Achillis forms a mass. Here and there are scattered tiny (? follicular) pits.

Histological examination of a section taken from the thigh shows slight acanthosis and spongiosis. There are patches of parakeratosis which appear to be localized mainly around the orifices of the hair follicles where a small vesicle is formed, containing polymorphonuclear leucocytes and a few horny lamellæ. The papillary body is œdematous. There, and in the subpapillary layer, is some round-celled infiltration, arranged diffusely around the vessels and also in small masses. There are no nævus cells.

From an examination of the section, I think that lichen planus can be excluded. The general appearance of the lesion is like that of a linear nævus, although the histological inflammatory changes are unusual. The hyperkeratosis over the tendo Achillis inconveniences the patient, and a single pastille dose of X-rays made no impression on it. I had thought of destroying it with diathermy, but would be glad of suggestions.

Discussion.—Dr. F. PARKES WEBER said his feeling was that this belonged to the class of case which Sir Jonathan Hutchinson used to call angioma serpiginosum, but the lesion, instead of being serpiginous, was linear. He would therefore call it a hyperkeratotic angioma serpiginosum. He thought the hyperkeratosis bore the same relation to the angioma serpiginosum that the hyperkeratosis bore to angiomata of the scrotum when (as not rarely happened) the latter were associated with hyperkeratosis and were therefore called "angiokeratomata". The chief change seen in the present case was the permanent dilatation of the cutaneous capillaries—a long telangiectatic line on the thigh and leg; part of this line was covered by hyperkeratosis and could, therefore, be called an angiokeratomatous (or angiokeratotic) line.

Dr. H. SEMON asked Dr. Parkes Weber whether it was not unusual for angioma serpiginosum to be localized in the way seen in this case.

Dr. PARKES WEBER agreed that it was unusual and said that one of its features was the gradual spread of the (angiomatous or telangiectatic) line in length.

Dr. SEMON urged that nothing should be done in the way of diathermy on such an exposed situation, where friction would irritate the resulting scar. It would be better to turn the case over to a surgeon to deal with by plastic measures.

Dr. BAMBER (in reply) said he did not agree with Dr. Parkes Weber.

? Ehlers-Danlos Syndrome (Forme Fruste).—J. H. TWISTON DAVIES, M.B.

This boy aged 8½ years, otherwise healthy, was first seen in February 1936, complaining of bleeding from vascular tumours on the knees. These had been appearing since he began to walk. An "angioma" was removed from the left knee by a surgeon in May 1934. A section from this showed large blood-filled spaces, new-vessel formation and much young fibrous tissue. Studied retrospectively it was partly responsible for a diagnosis of Kaposi's idiopathic sarcoma. Contemporary sections had the structure of a keloid, containing cyst-like cavities filled with blood, or empty and lined with irregularly proliferating endothelium.

The lesions undoubtedly disappeared under X-ray treatment and have not recurred. Moreover six months' treatment at a sanatorium for tuberculosis caused complete disappearance of symptoms, which did not reappear until seven months after his return. The disease has now reappeared in a modified form, consisting only of spontaneous hæmorrhages into the skin especially in the neighbourhood of the old scars and fragility of the skin covering the knees. There have been no more tumours.

Blood examination:—

Erythrocyte sedimentation rate	7 min.	Within normal limits by methods used
Coagulation-time	7 min.	
Bleeding-time	1 min. 20 sec.	

R.B.C. 5,088,000; Hb. 92%; C.I. 0·9: W.B.C. 14,400: *Differential.*—Polys. 44%; eosinos. 5%; small lymphos. 41%; large lymphos. 2%; hyalines 8%. Platelets 250,000. Fragility: Hæmolysis commencing 0·42 sodium chloride; complete 0·38 sodium chloride (same as normal control).

In spite of so much evidence of an infective or even a neoplastic nature, the case is offered, regardless also of the nearly complete absence of both cardinal symptoms, as an incomplete Ehlers-Danlos syndrome.

Dr. F. PARKES WEBER said that looking at the knees alone would cause one to think of the Ehlers-Danlos syndrome, provided the boy's history was known. There was evidence in this case that the lesions were traumatic and always bled, a fact which excluded the traumatic lesions of epidermolysis bullosa, which did not actually bleed. An American author[1] had recently pointed out that the chief sign or symptom of the Ehlers-Danlos syndrome was a friability of skin, and especially of the blood-vessels in the skin. This boy's knees evidenced that. But the other symptoms of the Ehlers-Danlos syndrome seemed to be absent; the boy had no lax articulations and no "cutis laxa" or hyperelastic skin.

He (F. P. W.) had recently had an opportunity of satisfying himself that the minute movable subcutaneous nodules or spherules met with in some cases of the Ehlers-Danlos syndrome, were not lipomata, as one writer had called them, but were true *arborescent* lobules of subcutaneous fat, which gradually became almost or quite separated, so as to form loose bodies in the subcutaneous tissue. At first they consisted of fat-vesicles in a fibrous capsule, but when they became quite separated from blood-vessels, the little spherules might consist only of a fibrous capsule with altered (fluid) contents.

[1] Ronchese, F., *Am Journ. Dis. Child.*, 1936, **51**, pp. 1403-1414.

Parapsoriasis Retiformis.—W. N. GOLDSMITH, M.D.

D. H., male, aged 34.

Present condition.—The skin of the chest and back is fairly evenly covered by an eruption arranged in a large-meshed network of dusky brownish-red streaks about 3 mm. broad. The surface is a little crinkled but not scaly. The skin within the meshes is normal. The eruption gradually fades off at its periphery towards the normal skin.

History.—Duration eight years, during which it has gradually spread. When the patient first consulted me on 26.8.37 he stated that it had always been itchy, but recently had become worse. He had been treated at the Allgemeine Krankenhaus in Vienna one year ago, where the condition was diagnosed as dry eczema. This suggests the probability of its having, at that time, been scaly.

Scrapings did not reveal fungus.

Biopsy (Dr. I. Muende):—

"The epidermis is thinned and the epidermo-dermal junction is flattened. There is no appreciable change in the stratum corneum. There is slight œdema of the pars reticularis, where there are roughly circumscribed areas of lymphocytic infiltration. The blood-vessels and lymphatics show marked dilatation.

"The histological appearances are compatible with the diagnosis of parapsoriasis."

Treatment and course.—The eruption has been aggravated by Whitfield's ointment and by tar, mercury, and salicylic acid ointment. The subjective symptoms have disappeared since the patient has been treated with liquefied phenol ½% in zinc cream.

Comment.—I believe this to be an example of the variety of parapsoriasis which MacLeod calls retiform, corresponding to Brocq's parapsoriasis lichénoïde, and which MacLeod considers the same condition as parakeratosis variegata (Unna and others) and lichen variegatus (Crocker). But the meshes are, on an average, much larger than those described by MacLeod who gives them as 2–3 mm. in diameter. The complete absence of scales is notable.

There are cases of this variety which can easily be confused with poikilodermia, especially in the absence of scaling.

Discussion.—Dr. GOLDSMITH: The eruption was somewhat unusual in having been intensely itchy; that symptom has now disappeared.

I ask whether any member has had experience in treating such cases with Grenz rays, which are reported to do good.

Dr. HUGH GORDON said that he had treated a patient of Dr. Roxburgh's with Grenz rays some five years ago. If the skin was sufficiently pigmented by the treatment the result appeared to be good. Unfortunately, in this case the patient had not been followed up long enough to establish the permanency of the results.

Dr. J. T. INGRAM said that some members had treated parapsoriasis with thorium X, with good results, and he would like to know whether those good results had been maintained.

Chronic Leukæmic Dermatosis.—W. N. GOLDSMITH, M.D.

D. F., male, musician, aged 43. Duration seven months. The condition began with irritation of the right arm. After scratching, angry red papules appeared, disappeared, and returned. The eruption spread to the trunk and after two months became pigmented.

When first seen by me four months ago there were, on the flanks, lower part of the abdomen, groins, and dorsal surface of the right forearm, dark mauve-brown, soft papules, roughly round in outline. There was ill-defined erythema and roughness of the axillary folds and flexural surface of the upper limbs. The left foot and lower part of the left leg were very œdematous and largely covered by confluent bullæ. There was much sodden peeling between the toes. The right foot was similarly, but less severely, affected.

There was enlargement of the femoral, inguinal, and epitrochlear lymph-glands.

The foot affection I took to be epidermophytosis and treated with monsol, 1 : 500 of water, followed by Castellani's paint and collosol sulphur internally. It cleared up with unusual rapidity and completeness. The flushing of the axillæ and arms also disappeared with simple local sedatives. But the remarkable pigmented papular eruption on the trunk gradually spread and became more irritating.

Wassermann reaction negative (12.7.37).

Blood-count (12.7.37): R.B.C. 5,940,000; Hb. 102%; C.I. 0·9; W.B.C. 10,900. *Differential:* Polys. 27%; lymphos. 35%; monos. 2%; eosinos. 36%; i.e. there was a moderate leucocytosis with great increase of eosinophils and moderate increase of lymphocytes. No mast cells.

10.8.37: Admitted as in-patient to University College Hospital. The pigmented eruption had extended over the dorsal surface of both arms and the lower part of the back. In addition small hard mobile subcutaneous nodules could be felt behind the right ear, in the right axilla, and in the right popliteal space. Itching was very severe. There were numerous small furuncles on arms and legs. Teeth badly infected. Tongue deeply fissured.

The eruption, though unlike anything I had hitherto seen, was, on the whole, most suggestive of lichen planus.

Biopsy (Dr. W. Freudenthal) :—

"Several biopsies were taken from various lesions, the histology of which is similar. The horny layer is either normal or shows a few parakeratotic cells. The rete, thinned in some places, is thickened in others, with the occasional formation of a small vesicle. Pigment is considerably increased. There is œdema in the papillary body and some of the rete pegs are flattened. The essential change is a strong infiltration of all layers of the cutis. The infiltrate, which is mainly around smaller vessels, some of which are newly formed, consists of round cells and a great number of eosinophils. In one section the sebaceous cells have disappeared from a small area near the wall of the gland and are replaced by round cells and eosinophils. A further biopsy was made from a pea-sized gland of the right groin. The cortical part, including germ centres, is normal or only little altered. In the central part is a proliferation of the reticulo-endothelial cells with numerous eosinophils. No reticulin production; no giant cells of any kind".

This ruled out lichen planus. The appearances indicated the possibility of its being a drug-eruption or a blood-disease.

Drugs were, as far as possible, excluded. The patient had taken Armstrong's blood mixture one year before the eruption, and Clark's blood mixture for a short time after its onset in May 1937.

As the blood-count was inconclusive, further light was sought by sternal puncture.

Marrow tap (Dr. J. C. Hawksley) :—

"A very cellular marrow.

	Per cent.		Per cent.
Stem cells	1·5	Eosinophil polymorphonuclears	10
Myeloblasts	6	Lymphocytes	2·25
Premyelocytes	6	Plasma cells	0·75
Myelocytes	10·75	Erythroblasts	8·5
Metamyelocytes	10·5	Normoblasts	7·5
Polymorphs	25·5	Megakaryocytes	0·25
Eosinophil myelocytes ...	9·25	Myelotic cells	1·25

The cellularity and relative immaturity of the myeloid cells is suggestive of a chronic leukæmic process, but might be an abnormal response to infection."

Stools: No worms or ova were found to account for the eosinophilia.

Treatment.—A few doses of X-rays failed to relieve the itching and the eruption seemed to spread rather more rapidly after them. The subjective symptoms have improved since the patient has taken ferrous sulphate and extract of liver.

Discussion.—Dr. F. PARKES WEBER said he saw nothing in the blood-counts of this case to suggest leukæmia of any kind. It seemed to him that it was more likely to be a case of eosinophilic Hodgkin's disease. But an allergic pruriginous eruption was sufficient in itself to cause enlargement of lymph-glands and local and blood eosinophilia.

Dr. J. T. INGRAM said he wondered if lichen planus could really be excluded by histological examination. The histology of lichen nitidus did not suggest lichen planus, yet those two conditions were intimately related. It would cause some surprise on looking through the *Proceedings* to find the cases shown as probable leukæmia, of which nothing further was reported. In this case he saw nothing to support the diagnosis of leukæmia and suggested that of prurigo.

Hodgkin's Disease with Erythrodermia.—J. E. M. WIGLEY, M.B.

G. H., male, aged 44, a farmer, admitted to my ward 4.6.37, with a generalized erythrodermia of some six months duration.

He stated that the eruption had been preceded by intense irritation, and appeared first on the bottom of his back. Then it appeared on the flexures, then on the thighs, and finally covered the whole body. He had noticed general enlargement of his glands about three months before admission, most marked in the groins. There are exacerbations of irritation, and the glands swell.

He was seen in March 1937 by his doctor who has kindly sent me these notes :—

"Widespread rash, showing the typical papules of lichen planus on the trunk, but also involving the arms and legs, where there was considerable exfoliation. He has had intense irritation and I did a lumbar puncture which relieved this to some extent. His general condition is fairly good. He has not had any arsenic, but has had twelve injections of colloidal calcium with vitamin D which have apparently done him good. There has been no rise of temperature and the weight has remained constant."

When I first saw him the entire skin was of a dark brick-red colour and felt thickened. The palms of the hands and the soles of the feet presented numerous painful fissures and a moderate desquamation. In other parts the desquamation was not marked. He was an "*homme rouge*". There was definite enlargement of the lymphatic glands in the neck, axillæ, and groins. A skiagram showed no evidence of enlargement of the hilar glands.

Otherwise physical examination was negative. The blood-pressure was 116/64. The Wassermann reaction was negative. The urine showed nothing abnormal.

Three blood-counts are as follows :—

	June 8	June 22	June 29
R.B.C.		5,320,000	5,180,000
Hb.		86%	
W.B.C.	18,100	17,600	21,800
Polys.	52%	60%	53%
Eosinos.	26·67%	24·34%	21%
Large hyalines	1·34%	2	3·67%
Small lymphos.			
Large lymphos.	20%	13·67%	22·34%

The sedimentation rate was "28 mm. in the first hour".

Histological report (Dr. I. Muende):

There is marked acanthosis, with lengthening of the rete pegs, absence of the stratum granulosum, and parakeratosis. The papillary vessels are very dilated, and the papillæ contain an excess of endothelial and lymphoid cells. In the sub-papillary zones there are very numerous circumscribed foci of epithelial cells, between which there are numerous lymphoid cells.

Gland.—The normal structure of the gland is destroyed owing to an overgrowth of the germ centres, resulting in proliferation of endothelial cells. There are numerous Dorothy Reed cells.

Dr. Mervyn Gordon has examined the sections and has kindly made the following reports :—

"The gland is almost certainly lymphadenomatous, as there is fibrosis and eosinophilia present as well as hyperplasia of the reticulo-endothelium with some giant cells. One would feel more certain if the latter were a bit more typical, but that does not invalidate the provisional diagnosis of Hodgkin's disease. The skin shows a few scattered foci that have eosinophils and an activity of connective tissue cells around them. This I think would do for a lymphadenoma metastasis in an early stage." (July 1937.)

Dr. Gordon began his biological test in September and wrote as follows :—

"The suspension of this gland has given a typical positive result (++) on the fourth day with all the syndromes in the biological test for lymphadenoma. This confirms the provisional interpretation of the histological changes in the section of both glands removed for biopsy, and of the section of skin."

During the patient's stay in hospital he had several exacerbations of his irritation, on two occasions followed by a rise of temperature, once to 101°, and once to 100°. The skin showed considerable improvement in colour and the fissures and desquamation of the hands became less marked. At no time was there marked desquamation of the body, or any evidence of moisture or weeping.

Dr. Mervyn Gordon kindly prepared a vaccine, which has been given weekly, in increasing doses, for the past three months, but since the patient left hospital the improvement has not been maintained. I am admitting him again to-day for further observation.

Dr. GOLDSMITH said it was interesting to see a case of Hodgkin's disease exhibited at the same time as his own case, especially as the diagnosis seemed to be well corroborated. In his own case, allergic prurigo had not occurred to him. All the nodules—unlike prurigo nodules—had a soft velvety feel. Moreover, the eruption had been relentlessly extending, though the itching had diminished. With regard to the eosinophilia produced by allergic prurigo, he was surprised how little there often was, especially in common urticarias, in association with which one, often, did not find any eosinophilia. The gland also showed eosinophilic infiltration, but nothing specially characteristic of Hodgkin's disease.

Acne Conglobata.—F. A. E. SILCOCK, M.D.

Patient, an unemployed miner, aged 57, married, seven children, says that, with the exception of hæmorrhoids, his general health has been good, except for the present trouble.

Left hand crushed in a brick press forty years ago ; amputation of left thumb and adjacent two fingers. Right forearm cut open by an accident in a colliery twelve years ago and had eight sutures inserted. Both these wounds healed normally and well. No history of skin trouble in the family. Treated for present trouble in Birmingham four years ago and was recently attending Burton-on-Trent Infirmary. Sent to see me at Leicester Royal Infirmary on 14.9.37.

History of present complaint.—Patient says that the eruption began, like an abscess under the chin, over thirty years ago and spread on to both sides of the face. He thinks the original wound was due to a cut by the barber in shaving. These abscesses kept on coming in different places—first in both armpits, then on the back and front of the chest and on the flanks, and finally on the scalp, the back of the neck, and both buttocks. The affected areas always discharged matter for a considerable time, some eventually healing after about two years.

Present condition.—Patient looks debilitated. Temperature varies between 99° F. mane and 100° F. nocte. He had slight albuminuria on admission to hospital a month ago, but this has cleared up. There appears to be a distinct odour of butyric acid associated with this case and I also noticed an identical aroma with the previous case of the same complaint, shown by me here on 20.5.37. Possibly this is due to the

breaking-down of the subcutaneous fat in the panniculus adiposus about the lesions of the acne conglobata.

There are some recent atrophic scars on the scalp. Both sides of the face are affected, the right showing a whitish, atrophic, reticulated-looking scar over the whole beard area, with many keloidal-like scars and small nodules, whilst the left is inflamed and shows a granulomatous-looking ulceration. The neck, both shoulders, both axillæ, back and front of chest, right side iliac crest region and abdominal wall anteriorly, as well as several small scattered areas over trunk generally, show localized patches of inflamed, slightly heaped-up, granulomatous-looking tissue, from some of which a little pus exudes.

Where the inflammation has died down or decreased there are several keloidal, bridge-like scars (Brückennarben of Lang). These are well seen in both axillæ and in the cruro-scrotal folds. On the patient's admission to hospital the axillary scars considerably interfered with extension of his arms above his head and he was not able to put on his own coat, but there has been considerable improvement since then and he has now almost full extension.

A section for biopsy was taken from the region of the right iliac crest.

Both buttocks, posteriorly, show an indurated, undermined, inflamed area, over which the skin is of a reddish-purple hue. This latter condition extends forwards on contiguous areas of the nates into both cruro-scrotal folds, forming marked fibrotic bridge-like bands there. An old external hæmorrhoid is present.

Wassermann reaction negative, 18.9.37.

Smears from the pus showed large numbers of polymorphonuclear pus-cells and a number of organisms, chiefly staphylococci but also large numbers of diphtheroid bacilli. No acid-fast bacilli were found.

Cultures, both aerobic and anaerobic, showed enormous numbers of cocci and bacilli, by far the most predominant organism being a short diphtheroid bacillus, some of these latter were Gram-negative, but I think they were all the same bacillus, the young ones not retaining the Gram stain.

Biopsy sections (from right iliac region).—These show an ulceration of the skin, and where the ulceration has taken place a large amount of pus of a polymorphonuclear type is present. Throughout the sections there are patches of inflammation, both in the rete mucosum and in the cutis vera, and these appear to consist of large connective tissue cells of an endothelial type, amongst which new blood-vessels are being formed and there are very few pus cells in these areas, either lymphocytes or polymorphs. No tubercle bacilli or any other organisms have been seen in the sections, nor have they the microscopical appearances of tuberculosis, and no giant cells are present. The condition appears obviously to be a chronic granuloma.

Treatment so far has consisted of eusol and antiseptic dressings, together with short-wave therapy to the septic areas, plus an iron tonic. I would welcome suggestions as to further treatment.

Discussion.—Dr. L. FORMAN asked whether this case might not be considered one of diphtheroid ulceration of the skin, since the bacteriological finding was a short diphtheroid bacillus. Cases of diphtheroid ulceration previously described showed a similar appearance of healing taking place behind an advancing granulomatous, hypertrophied edge.

Dr. A. M. H. GRAY said the case resembled one which he had shown a few years ago as a case of staphylococcal granuloma; the lesions on the face had been very similar to those in this case. It looked like a fungating sycosis. There were also lesions on the forearms, groins, upper abdomen and left shoulder. In that case the lesions could be reproduced by intradermal injections of the vaccine of *Staphylococcus aureus*, which, no doubt, was the causal organism.

He did not think that the present case should be entitled acne conglobata (he had not seen the case—only the photographs). He gathered that there were present none of the cysts or abscesses which were characteristic of that condition, but there were cellulitic abscesses in association with a diffuse staphylococcal infection of the skin.

Dr. SILCOCK (in reply) said he thought the essential features of acne conglobata were the bridge-like scars, the chronic undermining and the spreading of the lesions. In Michelson's and Allen's report[1] on the condition they described a scrofulodermatous or tuberculous aspect of the lesion, with absence of a tuberculous histology. This case showed all these features markedly.

Referring to Dr. Forman's suggestion, he had not yet had time to work at that, but attempts would be made to find whether a diphtheroid infection existed.

Scarring from Exposure to the Sun.—F. PARKES WEBER, M.D.

The patient, C. J. S. H., aged 25, a well-built man, has apparently been subject to a red inflammatory eruption every summer over the surfaces of the body exposed to the sun. As a result of this he has a good deal of scarring, especially over his ears and, to a lesser degree, over the back of his hands and his face. There is also some scarring about the knees dating from the time when he was a boy scout or wearing shorts.

Otherwise I find nothing abnormal. Never any obvious porphyrinuria. No history of any similar trouble in relatives. Is the skin-sensitivity in this case allied to that in xerodermia pigmentosa (Kaposi) ?

Discussion.—Dr. A. C. ROXBURGH said he thought that the patient had had blisters on his ears, because there were a number of small scabs there which looked like dried-up blisters. He thought this was a case of hydroa vacciniforme. Cases which showed hæmatoporphyrinuria were more severe than this one.

Dr. A. M. H. GRAY said he thought that cases which showed dark bones always had hæmatoporphyrinuria. A case which he had shown before the Section in December 1923[2] had shown that change in the bones very well. The teeth also were discoloured, but were not actually pink. He had suggested that another factor must be present besides hæmatoporphyrin. Cases had been reported in which severe scarring had followed hydroa, and no porphyrin had been discovered. Possibly in some of these cases there was present a congenital factor analogous to that in epidermolysis bullosa ; and the sensitiveness of the skin caused a reaction to light rather than to trauma. No one had yet published an explanation of the severe cases of hydroa which showed no porphyrin excretion at all. In people who had artificially sensitized themselves to porphyrin, the reactions were not as a rule like those of hydroa. There was, apparently, an epidermal rather than a vascular sensitiveness ; there were no deep-seated lesions causing bullæ and scarring. In eczema solare extensive blistering occurred, but scarring did not result.

Dr. G. B. DOWLING said that porphyrinuria might be present without a very marked degree of sensitiveness to light. He had under his care a case of porphyrinuria in an adult, in which bullæ developed each summer on the exposed parts, especially the backs of the hands and the neck, but these did not appear usually until July ; they disappeared in October, though the porphyrinuria was always present throughout the year.

Alopecia Areata in an Infant.—CLARA M. WARREN, L.R.C.P., M.R.C.S. (for R. T. BRAIN, M.D.).

This boy first attended the Skin Department at the Hospital for Sick Children, Great Ormond Street, at the age of fifteen months. He had had, for nine months, two typical patches of alopecia areata in the occipital region, where new growth of hair is already showing. There was no evidence of rickets, and the child had never suffered from head-rolling.

I have not been able to find a record of alopecia areata in so young a patient. At a meeting of the Section for the Study of Disease in Children in 1913 Dr. Poynton showed a case in a child aged 2 years who had had the condition for six months, and whose two older brothers were at the time suffering from the same complaint.[3]

[1] *Arch. of Dermat. and Syph.*, 1931, **23**, 49.
[2] *Proceedings*, 1924, **17** (Sect. Derm. 43) ; *Quart. J. Med.*, 1925, **19**, 381.
[3] *Proceedings*, 1913, **7** (Sect. Dis. in Child., 36).

Family history.—The paternal family history of the child shown to-day is of interest. His father, uncle, grandmother, and great-aunt all suffered from alopecia areata at some period in adult life, and it is remembered that the hair grew readily within six months with local treatment. Cases on record of alopecia areata occurring in three generations appear to be rare, although the hereditary influence is definitely recognized.

The PRESIDENT said that he had seen a case at the Royal Free Hospital in an infant less than a year old. He agreed as to the hereditary factor in alopecia areata, but the age at which this hereditary tendency might begin to show itself was remarkable. On the one hand, alopecia areata might appear in the first year of life; on the other, he had seen a man aged 77, in whom it had only just developed, although both his father and his grandfather had suffered from it.

? Lupus Erythematosus.—HUGH GORDON, M.R.C.P.

Patient, female, aged 30.

History.—Fifteen years ago the patient suffered from what was called septic arthritis of the hip. So far as could be gathered this was not tuberculous. Arthrodesis was performed and she now has a stiff hip. Two years and six months ago she had a child; the confinement was normal. For about a year she had what were described as "ulcers in the mouth" together with blepharitis. At about the same time the three lesions which she now presents appeared on her face. The one on her forehead was on the site of an old vaccination mark, the one on the chin on the site of an old boil, and the one in front of the left ear apparently arose on normal skin. Ten months ago she was given 12 injections of krysolgan at weekly intervals, a diagnosis of lupus erythematosus having been made. Under this treatment the blepharitis and sores in the mouth cleared up but the skin lesions remained more or less unchanged.

The patient was only seen for the first time three weeks ago, and X-rays 200 r were applied to the lesion on the chin. Since that time all the areas have improved somewhat, but there is no essential difference between the lesion that was X-rayed and the others. The lesion on the chin is 1 cm. in diameter and shows well-marked induration round the edges with a central depressed scar. The lesion on the forehead is essentially the same but smaller in size. The lesion in front of the ear shows an elongated scar with no induration. The patient states that no discharge or matter comes from the place though she has at times picked off some scales. There has, as yet, been no opportunity for a biopsy or other investigations.

Discussion.—Dr. J. H. T. DAVIES suggested excising the lesions; this procedure would leave less scar than any other form of treatment.

Dr. A. C. ROXBURGH said that he was not prepared to give a diagnosis, but he did not think it was lupus erythematosus—for one reason, because the scars were not produced by the disease, but the disease had begun around already existing scars (of chicken-pox and of a boil) which had been present for a long time.

? Darier's Sarcoid.—G. B. DOWLING, M.D.

Male, aged 60.

In May 1937 I was asked to see this patient—who had enjoyed good health all his life—on account of a number of tumour-like lesions which appeared first nearly a year ago. They were firm subcutaneous nodes, about 15 in number, and were present chiefly along the extensor aspects of the limbs. They began deeply and the skin could at first be moved freely over them, but later some of them involved the skin which became cherry-red or blue in colour. The patient had lost weight and had not felt well, though there were no special symptoms.

An excised tumour was found to have a tuberculous structure with many giant cells, but without caseation. X-ray examination of the small long bones was negative,

and there was no apparent enlargement of the glands or of the spleen. The lungs, however, showed dense mottling, suggesting bronchiectasis, though there had never been any pulmonary symptoms. There was no cutaneous reaction to the intradermal injection of O.T. 1 : 1,000.

I advised the Sauerbruch Herrmannsdorfer Gerson diet, as described in Dr. Goldsmith's book, and bi-weekly injections of sodium morrhuate. Whether as the result of this treatment or not, all the lesions have become smaller and some have disappeared. The patient has also regained his lost weight and feels very well. I am not sure whether the case is one of Darier's sarcoid, or one of Schaumann's disease.

Dr. GORDON said he felt that the mottling of the lungs pointed rather to Schaumann's disease.

Section of Otology

President—F. J. CLEMINSON, M.Chir.

[*November* 5, 1937]

Aural Vertigo: A Clinical Study

By A. J. WRIGHT

THE material for this paper consists of cases, seventy-three in number, which fulfilled the following two conditions :—

(1) The patient had consulted an aurist on account of vertigo.

(2) Middle-ear suppuration was not present.

Of these seventy-three cases the great majority, namely sixty-six, conformed to the general description which I am now about to give you. The remaining seven were oddments of known ætiology.

The clinical picture presented is as follows :—

Sex and age.—Males predominated in the proportion of forty-two to thirty-one, the average age-incidence being 47 years. Although the fully developed condition is not met with in young people, evidence will frequently be obtained, on careful investigation of the history, of some auditory disturbance dating back to early adult life. Only a few cases occur in old age, five of the present series being in persons aged 70 years and over.

Onset of the complaint.—The first symptom noted by the patient was, in more than half the cases, auditory and not vertiginous. Of the former (auditory) group, deafness was the initial symptom in one-third and tinnitus in the remaining two-thirds. Of the group in which auditory symptoms preceded the vertiginous, the interval which elapsed before the onset of vertigo was in all cases—with two exceptions—a period of months or years, up to a maximum of thirty years.

Hearing.—As far as the affected ear was concerned, some loss of hearing existed in all the cases except two, but in these two a history of temporary deafness during the attacks was obtained. The degree of defect in the affected ear was as follows :—

Useful hearing, i.e. perception for the conversation voice at 6 ft. and over, was present in rather less than half. Of the remainder, absolute deafness existed in nine and only a remnant of hearing persisted in a further twenty-eight cases.

In half the total cases the hearing in the unaffected ear was normal, and, in the other half there was a bilateral defect. Where the defect in hearing was bilateral, in eight cases it was extreme in degree, leaving no useful hearing.

Variability in the hearing was frequently met with, both according to the statement of the patient and to tests, a temporary depreciation preceding or coinciding with the attacks of vertigo. A history of paracusis, hyperacusis, and diplacusis was not uncommonly noted, particularly in the early stages of the disorder and preceding the acute vertiginous attacks.

Type of hearing defect.—In regard to tone loss, where this was accurately recorded, the upper portion of the scale was lost in eighteen, the lower portion in nine, and in twelve the defect was for all tones.

Correlation of hearing and vertigo.—The degree of loss of hearing was not found to be a reliable guide in estimating the prognosis as to the duration of the vertigo. Thus, in those cases in which the hearing had been entirely destroyed in the affected ear, in nine the vertigo still persisted and in only four had it ceased. Of those cases in which only a remnant of hearing remained, in eight the vertigo had ceased but in a like number it still persisted.

Vertigo.—With a few exceptions, the type of vertigo met with in the cases under review was severe in degree.

Excellent descriptions of the various types of aural vertigo exist in the literature, among which I may instance Mollison's at the Summer Meeting in 1935,[1] and I certainly could not improve on these. I should, however, like to emphasize certain characteristics which seem to me of importance :—

(1) The great variability met with in the frequency, severity, and duration of the attacks.

(2) The frequent occurrence of a more or less constant unsteadiness between the typical acute attacks of vertigo.

(3) The occasional occurrence of cases in which this constant type is the only one present.

(4) The widespread nature of the upset produced throughout the vegetative nervous system. Thus, for example, abdominal discomfort and diarrhœa are not infrequent and may occur without vomiting, leading to errors in diagnosis.

(5) While the subjects of this disorder are not particularly drawn from the neurotic type of individual, the complaint is, by its nature, so mentally disturbing and produces such a feeling of insecurity, that it is only to be expected that some subjective giddiness should sometimes tend to persist, for a time at any rate, as a functional manifestation, after the organic changes have ceased to progress, either spontaneously or as a result of treatment.

Tinnitus.—This was present in all cases, with one exception. It was extremely variable both in incidence and nature, an increase in degree usually preceding the vertiginous attacks. In addition to the tinnitus, a sensation of numbness or fullness in the ears was frequent, and occasionally this amounted, in the patient's description, to an actual pain. These symptoms displayed the same type of variability as the defect in hearing and the tinnitus.

The membrane and middle-ear.—The tympanic membrane on the affected side was normal in forty-eight cases. There was some degree of milky opacity in five, and, in nine there were more or less extensive post-suppurative cicatricial changes, with a dry perforation in three of these. In those cases with cicatricial changes, the minimum interval separating the onset of the vertiginous attacks from the previous suppuration was ten years. Three cases, all with normal tympanic membranes, showed bilateral hyperostoses, but they conformed in other respects to the general picture.

Eustachian tube.—The variation in hearing, alterations in sensation produced by inflation, and the effect of suggestion upon myself by the views of others, led me, in several cases, to suspect the existence of a pathological change in the Eustachian tube. In no case, however, on critical examination, was this suspicion confirmed.

Focal infective lesions.—One or more foci of infection were noted in all cases. These foci consisted of infected teeth, tonsils, antra, gall-bladder, and uterus. In one-third of the cases, more than one focus was noted. Dental, tonsillar, and maxillary antral infections were observed in great preponderance and, curiously, in absolute numerical equality. Of the antral cases, it is interesting to note that the infection was bilateral in six, on the same side as the labyrinthine lesion in five, and on the opposite side in an equal number.

Lesions other than foci of infection.—These were such as are usually met with in association with a focal infection, namely rheumatism, neuritis, acne of the face, nephritis, and iritis, in that order of frequency.

Course and duration of the complaint.—This is infinitely variable. Long periods of partial or complete freedom from vertigo may occur, perhaps alternating with attacks of extreme severity, and this fact renders it very difficult to assess with certainty the results of treatment.

[1] *Proceedings*, 1935, **28**, 1571.

While the complaint is a progressive one, as evidenced by the defect in hearing, such progression may be spontaneously and permanently arrested at any stage. As has already been stated, the duration of the disease is very variable, being, in my cases, between the limits of two and thirty-nine years.

Although there is a temporary ebb and flow in the course of the disorder, I have not as yet met with a case in which spontaneous cure has taken place, i.e. the vertigo and tinnitus have ceased and the hearing has returned to normal.

Conclusions.—As a result of this review I believe that we can recognize the picture of a *definite disease*. This picture, as seen by me, is of a chronic progressive lesion of the labyrinth, running a very irregular but long course, and always producing some permanent damage, as evidenced by loss of hearing. Though spontaneous cure does not occur, the disease may be arrested at any stage. The disease does not result from a lesion in the middle ear, but is primarily in the labyrinth. It is marked by an increased irritability of the labyrinth, as shown in (*a*) the cochlea by hyperacusis, and in (*b*) the vestibule by an abnormal reaction to normal stimuli (i.e. movements of the head) or to minimal abnormal stimuli such as some alteration of tension in the middle ear. The view that altered tension in the labyrinth accompanies the disease receives considerable support from the fact that lines of treatment, both medical and surgical, directed towards its readjustment, do alleviate the symptoms. In addition, focal infection is invariably present, and frequently there exist in the patient other lesions such as we are wont to associate with such infection.

Is there any other disease presenting a similar clinical picture? I believe that we find such a one in the case of *chronic iritis*. This complaint is also intermittently progressive, runs a long course, always leaves some permanent damage behind it, and is also usually unilateral. It is accompanied by increased irritability and an increase in tension in the eye, and measures designed to reduce the tension relieve the irritability and pain. Finally, the incidence of chronic iritis is roughly similar to that of the disease which we are considering. We can, however, in the case of iritis, actually observe the pathological process in the eye and appreciate that it is inflammatory. The only interpretation that I can make as a result of these observations is that we are dealing with a chronic inflammatory lesion of the labyrinth, secondary to a focus of infection.

How far do the effects of the eradication of the infective foci in such cases support this hypothesis? My results are as follows: All cases treated in this way, i.e. by eradication of a septic focus or foci, have been included, and, with one exception which is mentioned below, they are all now completely free from vertigo. The total number is twenty-three and, of these, in ten what may be described as a cure resulted, i.e. both the cessation of the vertigo and the return of the hearing to the normal. In a further three, the vertigo ceased and some improvement took place in the hearing. In nine, the vertigo ceased but the hearing remained unaltered. In one case the period of time since the operation is too short (four months) to estimate the final result, but there has been a progressive diminution of the attacks, with none for the last two weeks, and the hearing has returned to the normal.

I feel that although the number of cases is small, in view of the fact that all are included and that the results are so uniform, one must regard them as wholeheartedly supporting my hypothesis.

To sum up:—

I believe that cases of labyrinthine vertigo which have been regarded as of unknown or doubtful ætiology can all be grouped together as belonging to a single disease which I venture to call "focal labyrinthitis". This disease, I suggest, is an inflammation of the labyrinth. I base this view on the occurrence of nerve irritation, both auditory and vestibular, signs of tension and progressive loss of function, and the analogy with a known inflammatory lesion—chronic iritis. It is not, in my opinion, the result of disease in the middle ear. That it is secondary to a focus of infection is shown by

the invariable presence of such focus and, to a greater degree, by the arrest, or even cure, of the disease when such focus is eradicated. Finally this is, I believe, the only hypothesis which will be found to explain the many isolated observations in the literature which do not fit into our present somewhat indefinite ideas of its pathology.

Discussion.—Mr. W. M. MOLLISON said that Mr. Wright had advanced a very sound hypothesis.

He (the speaker) suggested that there was another group of cases, not included in the paper, namely, those of vertigo with variable deafness, the deafness being worse during the attacks of vertigo, and disappearing between attacks. It was his own experience that these occurred in young people, rather than in those of middle age and older, and were probably migrainous, as had been pointed out by Dr. C. P. Symonds. A case of interest in that connexion was the following:—

A man, aged 27, sent to him by Dr. Symonds because of very severe vertigo which completely disabled him from his work, brought the request for destruction of the labyrinth. Hearing at that time was normal on both sides, therefore he had been obliged to reply that it was impossible for him to decide on which side to operate, and he had to decline to do so. Dr. Symonds had kept the man under observation, occasionally sending him to him (Mr. Mollison), still with the hearing normal, though said to be diminished in the right ear during the attacks. But on one visit hearing on the right side was found to have disappeared, the vertigo persisting. Destruction of the right labyrinth by operation completely cured the vertigo.

Mr. MUSGRAVE WOODMAN said that he entirely agreed as to the desirability of removing the foci of infection, and felt sure that this method of treatment did a great deal of good. But the removal of such foci only did not cure the majority of his cases. Sufficient notice had not been taken with regard to water metabolism.

In Copenhagen a great deal of attention was paid to this condition. He did not think that many such cases occurred in this country, but he had had personal experience in his own family of a patient who complained of deafness and tinnitus and œdema under the eyelids. On investigation it was found that she drank large quantities of plain water daily, and a drastic reduction of the water intake not only removed the bagginess from under the eyes, but restored the hearing to normal and cured the tinnitus.

It was important to consider the condition of the Eustachian tube, to which attention had been called so often by Sir James Dundas-Grant. Was it sufficient to rely on the passage of a Eustachian catheter only? In his own cases he found the use of a Eustachian bougie invaluable, and the majority of cases of vertigo could be cured by this treatment alone.

The prognosis in cases of vertigo was good. The majority responded to the removal of septic foci followed by the careful passage of a Eustachian bougie to the affected ear.

A few cases remaining had proved obstinate, and these had been submitted to Portmann's operation. After having seen this operation performed at Bordeaux he (the speaker) had attempted it in a difficult case which had resisted all treatment for two years. It was in a young man unable to work because the vertigo was so bad that it caused him to fall in the street. After the operation he had no further attacks and completely recovered. He (Mr. Woodman) had carried out the operation in five cases; in four the patients had been completely cured and in the fifth the condition had been improved.

The essence of this operation was to lift up the dura mater from its normal adhesion to the aqueduct of the vestibule. At the moment this was done, a drop of clear fluid often exuded from the foramen. The dura was then laid back in its place and acted as a valve. It was a satisfactory operation, but one only to be performed in cases which resisted the more simple methods of treatment.

Mr. C. S. HALLPIKE said that Mr. Wright's view of this syndrome as being of focal infective origin was supported by the evidence he put forward, but he did not understand why the reader took the view that the impact of the focal infection was on the labyrinth rather than on the 8th nerve. Dandy, who had written largely on the subject, took the view that the causal lesion was somewhere in the 8th nerve, and that authority's operative treatment was based on that idea. Would it not be possible to read the evidence as supporting the view that the lesion was in the 8th nerve?

Another point concerned the normality of the ear drums, and the bearing of that on the normality or otherwise of the middle ear and Eustachian tube. Dandy's cases had been examined for middle-ear disease, and the reports seemed to show that at any rate the ear

drum was normal. He thought that a good deal of evidence showed an abnormality in the middle ear in many of these cases. Abnormalities were, however, difficult to assess.

Mr. THACKER NEVILLE said that he had cured cases of vertigo by removing the tonsil; a man who was driving his car from one side of the street to the other had been cured in that way. He had cured a few such patients by correcting the water metabolism. These formed a type by themselves; they had thick subcutaneous tissues. Sometimes the physician could "spot" a man with faulty water metabolism by a glance at the back of his neck. Often he had rheumatism, and usually bone-conduction was absent when tested with an a_1 fork. A case of this kind had been that of a police officer who sat in his office taking frequent libations of tea, which was kept infused. Years ago Mr. Sharp had shown that drinking quantities of tea was a cause of vertigo. The important point was the *quantity* of liquid imbibed.

He (the speaker) was following Mr. Mollison's work, and had carried out a number of injections of the 8th nerve, through the labyrinth. He had had a few cases of paralysis of the 7th nerve. He did not think that was because he had damaged the 7th nerve at operation; there seemed to be an overflow of the alcohol to that nerve. Alcohol injection was an easy operation, and there was a type of case in which no focus of infection was found, and there was no faulty metabolism; in these Mollison's procedure had a marvellous effect.

Mr. WATKYN THOMAS said that an objection to Dandy's view that Ménière's disease was due to a lesion of the nerve-trunk or the ganglion was that many cases which had resisted all other methods of treatment had been completely cured by destruction of the labyrinth by alcohol injection or otherwise. This showed that in these cases at any rate the causal lesion could not be central to the labyrinth.

Among his own cases at least one-third showed Eustachian obstruction, as proved by the Valsalva test.

As to the failure by water-shortening methods, he did not think the same type of case was met with in this country as in Copenhagen. He suggested that this was due to the enormous salt consumption in the diet in Northern Europe.

Mr. A. D. SHARP said that, with reference to the case which he had reported many years ago, in which the patient drank excessive quantities of tea, it was not correct to attribute the symptoms to the *amount* of fluid taken, as distinct from the tea. The patient was a hospital matron who had suffered severely from vertigo, and was much concerned because of the possibility of losing her post. She was an addict to strong tea and consumed a large quantity daily. His view was that the vertigo was due to the tea toxin. When advised to give up the tea she said she must have something to drink, so he advised her to try a brew of ginger or something similar. She did as advised, and in six months she was free from the vertigo, though she continued to take as much fluid as before.

A little more emphasis should be placed on the effect of removing a nasal block and so relieving the Eustachian defect. Some years ago an engineer from Egypt had consulted him on account of very severe vertigo which had made him afraid to go amongst machinery. He had a blocked nose, owing to a deflected septum. He (Mr. Sharp) had advised operation, giving a hopeful prognosis, and had sent the patient to Mr. Sydney Scott, who agreed with this view. He (the speaker) had operated, and in six months the patient had returned fit for duty, and had no further trouble.

Mr. WRIGHT (in reply) said that it was difficult to go further without writing a book on the subject.

The treatment referred to in the paper was the removal of a septic focus, or of septic foci, and all the cases which had been so treated were included in the results. He disagreed with Mr. Mollison in regard to his migraine group. The invariable loss of function, as shown by a defect in hearing in the cases under review, seemed to him to rule out Mr. Mollison's hypothesis.

The theory of a defect in water metabolism was, to his mind, very unconvincing. The idea that an excess of intake of water could produce these changes was difficult to believe. He suggested that an examination of the literature would show that the many conflicting findings and views as to the pathological condition would fit in with the conception of a chronic progressive inflammatory lesion in the labyrinth.

Mr. Hallpike had raised the question as to whether the lesion was in the labyrinth or in the auditory nerve. His own view was that all the evidence supported the labyrinthine nature of the complaint.

DISCUSSION ON SEASICKNESS

Opening Papers

(1) The Cause of Seasickness

By T. Gwynne Maitland

Of the symptoms, vertigo, nausea, vomiting, and prostration, denoted by the term "seasickness", one only—vertigo—demands notice in any attempt to understand the essential and underlying features and source of this malady.

The other symptoms are common to many ailments, but have no special significance other than that they are an expression of an acute perceptuo-emotive experience.

There is no essential difference between the symptoms of seasickness and those of air, train, and swing sickness; they are all consequent upon some form of passive displacement and the prominent symptom in all of them is vertigo.

Passive displacement, called also imposed movement or deposition, is one of the problems connected with the maintenance of equilibrium. The maintenance of equilibrium is a primitive and vital necessity, making possible all purposive activities such as the acquisition of food, the attitude of attack and defence. The specific physiological response of failure is called disorientation—the psychological, vertigo.

Vertigo is occasionally found to accompany conditions other than equilibratory dysfunction, such as constitutional, toxic, and traumatic, but its immediate precursor is invariably some interference with the centres controlling equilibrium, however primarily caused.

The terms disorientation and vertigo require definition.

For physiology the terms orientation and disorientation mean the reactions which respectively maintain, or fail to maintain, equilibrium. They are not synonymous with the terms co-ordination and inco-ordination, as these latter have not the wide spatial reference to the body as a whole, and its equilibrium, but refer rather to the harmonious or inharmonious action of parts of the body, as to their proper order and sequence.

The muscles of the body, whether engaged in moving an arm or leg, or in the production of speech, or governing the pupil, are planned on an "action system" by the inherited organization to bring the whole body, or any part of it, into accord with the extra-bodily world.

Though the skeletal muscles are voluntary they perform their vital role in the maintenance of equilibrium by acting automatically or reflexly as an action system. In self-propulsive movement, such as walking, the initial effort is a voluntary one; the subsequent movements may or may not become automatic. At any stage an act of will may intervene and cause speeding up, stepping aside, or halting.

As distinguished from self-propulsion, any tendency to movement under passive displacement is compensated by "an action system" of simple stato-kinetic reflexes, whereby the body becomes orientated. There is no conscious awareness whatsoever of this bodily reaction when competent. If the passive displacement is of such a kind as to cause disorientation then, and then only, is there awareness of disordered equilibrium. This awareness is what is termed vertigo.

In the accompanying attempt to consider the consequence of disordered equilibrium in the human subject, it is to be understood, therefore, that "disorientation" is intended to express the physiological reactions, and "vertigo", the psychological reactions.

The causal relations of disorientation and vertigo are not generally understood. The naive opinion is that vertigo is an antecedent to disorientation, in other words, that mental perplexity and confusion regarding one's position in space make it difficult or impossible to keep one's balance.

Disorientation, like orientation, occurs, however, in decerebrate animals, whereas vertigo, as a perceptuo-emotive experience, depends upon the possession of cortex and thalamus. That does not, however, dispose of the fact that when vertigo arises as a consequence of disorientation it, in turn, aggravates disorientation by exciting voluntary effort to correct an illusion of deposition where no deposition exists.

Vertigo, furthermore, as the conscious awareness of disorientation, has a biological significance, in that when it is due to a failure to compensate some mode of passive displacement, it may be assumed that such a mode of displacement does not belong to the monotonous order of external agencies on which the inherited organization of our unconditioned reflexes has been built up. Thus it is that vertigo is excited by modes of passive displacement quite modern compared with our age-long history, such as by cars, by aeroplanes, by boats, roundabouts, and swings.

The awareness of disorientation indicates the breakdown of routine.

The modes of passive displacement can be reduced to two—rectilinear and angular. All the modern forms of locomotion which cause disorientation are found to exhibit one or other or both modes. The best examples of rectilinear passive displacement are found in movement in lifts or in coal-shaft cages. The best example, angular, is of course in the experiment of the Bárány chair. The reactions to each of these has certain differences, so notable as in themselves to indicate without prior knowledge the mode of passive displacement, whether rectilinear or angular. The one is described as "special vertigo", and the other as "general". General vertigo is the more common experience under conditions other than experimental, it is characterized by dizziness with a visual illusion of approach and recession of objects. Special vertigo, on the other hand, is characterized by the illusion of subjective or objective turning. From the clinical evidence it may be assumed that the ship movement, with its roll or pitch of large amplitude, corresponds to the rectilinear order to passive displacement; that applies equally to the movement of swings and, for the most part, to the movement of aeroplanes.

The control of equilibrium consists of widely distributed and apparently unrelated factors. On the one hand there are the exteroceptors, consisting of visual sensations, pressure sensations from the supporting structures, and, to a lesser degree, auditory sensations; on the other there are the proprioceptor impulses which come from the labyrinth, the extra-ocular muscles, and the muscles, tendons, and joints of the neck, trunk, and limbs. These are all centrally related and all react on each other with certain reservations. In the course of experiment and observation some are found to play a major part, others a minor part, for which there may be vicarious substitutions.

The most responsive of all these factors to the condition now under consideration is undoubtedly the labyrinth, which is the chief receptor of passive displacement. The obvious difference between the impulses from the labyrinth and those from the cochlea and retina is that vestibular impulses do not, like the latter, pass to the cortex, but go through the lower cell stations to the extra-ocular muscles of the eyes, and the muscles of the neck, trunk, and limbs. The physiological character and field of response of the labyrinth has been determined by an age-long history of racial exposure to certain stereotyped modes of passive displacement, and for that only are they competent. They are not inert and passive to modes of displacement other than these—on the contrary they react abnormally, and in the case of the semi-circular canals actually cause disequilibration of a pronounced and specific type. This eccentric behaviour is, of course, a subject-matter for otologists, but it has a

profound significance in the comprehension of the physiological character of disequilibration. In the experiment of rotation which ultimately induces abnormal reactions there is only one phase which one can confidently predict is normal, and that is the initial response when the body and eyes compensate adequately the angular displacement. Beyond this point, with acceleration continuing, the compensation continues, but is inadequate, since it does not rectify and bring to rest the body—secured as it is in the rotating chair. After a certain time, when the inertia of the endolymph has been overcome, there is a condition of relative rest as between endolymph and ampullæ, impulses therefore ceasing to be excited by the ampullæ deviation of body and eyes in consequence also ceases. By means of the photo-electric cell, the pad on the closed eyes, and the necessary recording apparatus, it has been possible to show that nystagmus ceases, as it has also been possible to show, when by de-acceleration the dynamic conditions in the vestibule have been reinstated, that nystagmus recurs, but now in a direction opposite to the direction at the inception of movement. Nystagmus continues for some time after rotation has been completely stopped, having regard again to the inertia of the endolymph. Post-rotational nystagmus and deviation do not, therefore, depend upon external displacement, but depend on a residual disturbance in the vestibules.

The body therefore also exhibits definite signs of disequilibration ; it deviates, and possibly falls. This is called physiological disorientation, but the muscles which deviate in response to the vestibular impulses awaken proprioceptor impulses from within those muscles, the tendons, and associated joints. These proprioceptor sensations clash with the gravity sensation of pressure from the surface integument. At the end of rotation, if severe, the body, unless supported, falls in consequence of reflex deviation. It is, in fact, similar to the experience of pushing violently against a shut door when the resistance behind it is suddenly removed.

The reflex deviation is not the whole story ; the perceptual element of vertigo contributes its part to the fall. Though the body deviates, or is falling in one direction, the illusion is that it is falling in the other direction and the biological voluntary response is to correct forcibly the illusory deviation and not the real one, so it is that there is an added violence to the fall.

The result of a spin, in the case of a novice in the air, is that after centring his stick he has to deviate it again, thinking he is correcting a spin in the contrary direction. We are compelled by this evidence to concede that the semicircular canals are competent only for deviation of small excursion.

How far does the motion of a boat influence the canals ? It is difficult to say. If they play a part in disorientation it is a minor one, since the movement, for instance of the roll upwards, should counteract the movement downwards. We know in the case of the Bárány chair, that if, after stopping rotation, the chair is immediately reversed, usually for one turn only, all deviation stops and with it all vertigo. A consideration of the physical conditions within the canals enables us to predict this.

It is in consequence of these facts that attention is being turned more and more to the utricular otoliths. The postural reflexes of the otoliths have been determined, but the part the utricle plays in rectilinear movement is still uncertain. The dog, when its body is supported by a cradle, reacts to a sudden drop by an extensor response, i.e. dorsiflexion of the head and extension of the limbs : when suddenly raised, it reacts by a flexor response, i.e. ventroflexion of the head and flexion of the limbs. This is said to persist in the guinea-pig after the otolith organs have been disorganized by centrifugalization. Doubt has been expressed as regards the complete success of this method. Is this a valid reason, in any case, for assuming the semicircular canals to be, if indeed at all, the sole receptors for rectilinear movement ? We cannot exclude the possibility that the pressure sensations transferred from the pads of the feet to

the body when the dog is thus suspended may not be adequate to cause these responses when the pressure is suddenly withdrawn or increased, as the case may be.

In the long descent of an express lift, when the moment arrives for de-acceleration we experience the illusion of ascending, as the pressure sensations through the feet are just those we would feel in an actual swift ascent. Vice versa, in the de-acceleration after a long and swift ascent there is the sense of descending, since the pressure sensations through the feet come now from a negative phase de-acceleration.

There is, however, an important clinical observation which, in the absence of other indisputable evidence to the contrary, points to the possibility that the otolith organs may bear some responsibility for these illusions, even if they play no part in compensation to rectilinear passive displacement. It is well known that the sense of vertigo in a swift lift can be mitigated by depressing the head at right angles to the vertical. That would place the otolith organ in the so-called neutral position where vertical rectilinear movement is ineffective.

To revert to the dog and his extensor response, it is said that this response is protective, preventing the crushing of the body when falling vertically downwards. This cannot be true of man, since the extensor response would be the most certain way of causing disaster through the long axis of the body to the base of the brain. Man, to avoid this, invariably, when he jumps voluntarily, alights in a relatively flexed position. May not the vertigo arise from the conflict of the acquired conditioned protective reflex of flexion with a vestigial unconditioned reflex of his four-footed forbears ?

Taking into consideration the head position with reference to the rectilinear movement, one of the reasons for assuming that the movement in a swing is rectilinear rather than angular is that depression of the head again mitigates vertigo. If the semicircular canals were the receptors for disorientation in the movement of swinging, then depression of the head ought certainly to aggravate the vertigo, since it would transfer the direction of imposed movement from the horizontal to the vertical canal.

There is also another point against canalicular responsibility : it is that the movements of a swing to and fro do not annul the vertigo, whereas, as we know, reversing the rotating chair does so.

Experiments on a large number of subjects reveal the following to be the usual experience under angular and rectilinear movement :—

ROTATION, ANGULAR MOVEMENT

	Vertigo (special)
Inception	Nil
Acceleration	Nil
Uniform movement	Nil
De-acceleration	Slight
After sudden cessation	Severe

MOVEMENT IN A SWIFT LIFT

	Vertigo (general) Ascending	Vertigo (general) Descending
Inception	Moderate	Severe
Acceleration	Moderate	Severe
Uniform	Nil	Nil
De-acceleration	Moderate	Moderate
After sudden stop	Nil	Nil

The vertigo of rectilinear and angular movement differs not only with regard to perceptual character but, definitely and illuminatively, with regard to phase.

Bearing these facts in mind it appears that, though the chief onus of seasickness is still borne by the labyrinth, the weight of evidence seems to point to the utricle rather than the semicircular canals as the chief offender.

(2) Seasickness and the Vestibular Nervous System: Some Theoretical Considerations

By H. V. Forster

Seasickness, with its train of unpleasant sensations and physical signs, resulting in the final act of vomiting, is the reaction of susceptible individuals to a disturbing and unusual environment. If a relatively small proportion of passengers at sea in rough weather shows the fully developed clinical picture of the malady, there is little doubt that many of them do experience symptoms which interfere with their internal comfort and well-being.

I propose to analyse briefly the various types of motion which induce seasickness. When a ship is driven into a head sea, a passenger in a cabin well forward of amidships experiences the scend, and then the fall or pitch, which can be very distressing. When the ship is running before the storm, with the seas on the quarter, she will roll, and this will be her motion too when they are a-beam. Speed in a following sea may aggravate rolling, but the unhappy passenger will at least have the consolation of knowing that he will arrive earlier in port.

Some people will say they do not suffer unless the so-called corkscrew motion develops, which is a combination of rolling, pitching, and yawing, and to this complex motion is sometimes added the quaking of the ship in her length as she is wrung by the seas.

It is also said that the sudden movement or "lurch" of a vessel is particularly distressing to some passengers and I gather from a quotation by Keevil that Montaigne was particularly affected by it [1].

The otologist may see in this abrupt movement one of quick tilting, which will be a test of the efficient interaction of the utricle and the vertical semicircular canals in maintaining equilibrium, but on the other hand, such an abrupt stimulation of the vestibular nervous system also produces, as Kotyza has shown, an increase in the tonus of the vegetative nervous system and, above all, in what is called the parasympathetic.

In writings on the subject of seasickness—for example those of Keevil, Maitland, and Hill—we see particular attention given to the individual type of clinical pattern which emerges from the complex reactions of the vegetative nervous system.

The sufferer may express reactions of the vagotonic type, the sympatheticotonic type, the hyposympatheticotonic, or the amphoneurotonic type; thus it is the individual who is to be treated rather than the disease.

In considering the theories of the causation of seasickness, Keevil suggests that the so-called mechanical theories, which include movements in the semicircular canals are now largely discredited [2].

To the otologist interested in the vestibular apparatus, this is perhaps disappointing. He knows that the proprioceptors of the muscles and joints of the body segments are being actively stimulated in rough weather and the end-organs of contact and the distance receptors of sight, smell, and hearing, but also the labyrinth, which is the chief proprioceptor of the leading segment of the body, which is the head. "The labyrinth keeps the world right side up for the organism by keeping the organism right side up to its external world" [10], and it will be agreed that the vestibular apparatus of the passenger at sea is called upon to perform a difficult task and, in the susceptible individual, may play a considerable part in determining that confusion in the vegetative nervous system that ultimately results in the syndrome of seasickness.

Early instruction in physiology taught some of us that the labyrinth was concerned

with seasickness, and that deaf-mutes were not so susceptible as normal individuals: as evidence of arrested labyrinth development in the deaf-mute it was explained that if such an individual were blindfolded and then plunged into water in a swimming-tank his sense of disorientation could be particularly distressing. For the passenger with a healthy vestibular apparatus the deck of a ship provides a horizontal plane subjected to complex movements which I have already described, and I will recall some of MacNally's observations on the labyrinth because they explain how nausea may be produced when this apparatus is disturbed.

He points out that the labyrinth is designed so as to be stimulated by any movement of the head in space, and explains how the reactions which result from such stimulation of the labyrinth are compensatory and are intended to return the body, head, and eyes to their original position. To bring about this result the necessary muscle groups are stimulated and the sympathetic and parasympathetic nervous systems are notified to make the necessary preparations in the way of extra blood supply for the muscles, nerves, &c. that will take part in the adjustment. In addition there is a message sent through to consciousness that the head has been moved.

If the labyrinth is stimulated by anything other than active movement of the head—as for instance when the fluid in the semicircular canals is artificially moved during the caloric test, the central nervous system does not discriminate between this and a true head movement, with the result that the stereotyped set of reactions are called forth to meet an emergency which has not arisen. Amongst the confusion which takes place, the sympathetic readjustments result in excessive flushing, perspiration, and nausea [3].

It might be argued that it is unreasonable to compare caloric stimulation of the labyrinth with the stimuli provided by a ship tossed by the waves, but here we certainly have passive movements of the head in many directions and so persistently repeated that in sensitive individuals the vegetative nervous system will be actively engaged to the point of confusion.

In a recent communication Kotyza has written on the influence of the vestibular apparatus on the vegetative nervous system, and though his observations were made during the rotation and caloric tests, I believe they can help in this discussion.

He recalls that the vegetative manifestations supposed to result from labyrinthine excitation have been studied by Spiegel, Ledler, Allers, Ivamoto, and others, and that they include lowering of the blood-pressure, short inspiration and prolonged expiration, very energetic contractions of the longitudinal muscle of the walls of the small intestine, and increase in their tone. Kotyza himself examined in man the influence of artificial stimulation of the labyrinth by making use of the so-called oculo-cardiac and solar reflexes, and concluded that the vestibular apparatus exercises a considerable influence on the vegetative nervous system, and further that the stimulation of the labyrinth by rotation is more obvious than that called forth by the caloric test; the sudden stimulation of the vestibular nervous system will increase the tonus of the vegetative nervous system, and above all what is called the para-sympathetic. The minimum stimulation of the vestibular nervous system, according to Kobrak's method, will decrease the tonus of the vegetative nervous system [4].

This final expression of Kotyza's conclusions recalls some observations made by Hill in his essay on the care of the seasick, though he is more concerned with the problem of therapeutic adaptation, whether the stimuli be vestibular, visceral, or vasomotor, &c. "A second factor in the determination of the type of individual response appears to be suddenness or otherwise of the onset of disturbing stimuli.

"My experience suggests that when the disturbance arises suddenly it arouses responses which are predominantly vagotonic, whereas if it begins gradually and is continued for a relatively long period, the responses tend to be sympatheticotonic. This observation is also made with the reservation that most cases are of a mixed type" [5].

If we look for experimental information of the possible influence of labyrinth disturbance on the movements of the alimentary canal, we will find a description by J. le Huex and A. de Kleyn of their experiments on unilateral labyrinth extirpation in cats. They remind us that from clinical observations we know that changes in the function of the labyrinths are often accompanied by disturbances of the movements of the alimentary canal. It is, however, a remarkable fact, they say, that but few experiments have been carried out to investigate the problem.

Kremer and Spiegel, and Demetriades, have described experiments in which they have observed an increase in the contractions of the stomach and the loops of the small intestine after caloric stimulation of the labyrinth. Le Heux and de Kleyn, however, in their experiments, had the advantage over earlier observers of the examination of the movements of the alimentary canal, in using X-rays after the well-known method of Cannon, thus preserving natural conditions during the experiments.

After unilateral labyrinth extirpation in the cat the movements of the stomach are very feeble during digestion, those of the small intestine less influenced and those of the large bowel still less affected. The same result follows bilateral labyrinth extirpation, and they conclude that the loss of function of the labyrinth causes these disturbances of mobility. They also promised the future publication of their results of an examination of the nerve paths conveying these influences from the labyrinth and also the effect of certain drugs on them [6].

In his article " Health Cruises and Prophylaxis in Seasickness," Gwynne Maitland points out that in the year 1933, of the recorded cases in one large company, the average percentage for the fifteen voyages in the express giant liners was only 0·8%, and in the worst voyage of that year it was only 8·7%. He admits, of course, that these were recorded cases, consulting the ships' surgeons [7].

As Maitland believes that " To informed opinion seasickness is an expression of the failure of equilibrium ", it might be asked what kind of unpleasant sensations are noticed by susceptible healthy individuals when the labyrinth is experimentally stimulated and what percentage experiences them. An answer is to be found for example in a publication by S. H. Mygind [8], though he refers only to the commonly used method of rotation. In his examination of the vestibular reactions in normal young trained soldiers, Mygind found that only 34% felt a post-rotatory giddiness, and in many cases only after repeated experiment. Four only out of seventy of them had considerable giddiness, and in only two of these was this associated with general malaise during the rest of the day. Vomiting only occurred twice. Three of the men felt giddiness without having any sensation of rotation, which proves that a vestibular giddiness need not be connected with such sensation.

If we inquire whether sensations of giddiness are experienced by the seasick, we are informed by those in a position of authority that giddiness is sometimes complained of, but not often. The otologist may also ask whether nystagmus takes place. I am informed, however, that it is not recognized as a definite physical sign and we would not expect it to be, under such conditions. Dohlman's explanation of the working of the cupula of the ampulla of a semicircular canal may help us to postulate why nystagmus does not arise, and one of the results of Steinhausen's laboratory experiments on the labyrinths of living animals is this : " That a brief displacement of the cupula occasions only a deviation of the eyes, but a longer lasting displacement causes a nystagmus " [9].

Conclusions

(1) In preparing these remarks on seasickness I have assumed that the otologist may inquire if stimulation of the labyrinth exerts any influence on the development of seasickness.

(2) The labyrinth, according to Sherrington, is the chief proprioceptor of the leading segment of the body which is the head [10], and we expect that in rough

weather at sea it will be actively and persistently stimulated by movements of the head in space.

(3) Some evidence from the clinic and the laboratory has been quoted to show first, that stimulation of the labyrinth may have a marked influence upon the vegetative nervous system, and secondly, that the labyrinth exerts an influence on the movements of the alimentary canal.

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Mr. E. Watson-Williams said that the experimental findings in sea and train sickness were supported by clinical observation of the influence of age. Children were little affected by rotation: indeed, rotation to the point of giddiness was the essence of many childish games. But the young were susceptible to to-and-fro and rectilinear movement: they were easily made sea or train sick. As they grew up, they tended to "grow out of" this susceptibility: but instead, the adult was readily upset by rotation. A child on his way to the fair might be sick in the car, but if he took his father on the roundabouts it was the father who suffered, the child meantime thoroughly enjoying himself. The inference was that rectilinear and rotational movement affected two distinct systems.

Mr. D. A. Crow (Brighton) said he thought it would be agreed that the labyrinth was responsible for seasickness; it might be impossible to stabilize the labyrinth, but an attempt should be made to do so, though, of course, neither the up-and-down displacement of the ship, nor the side-slipping movement could be overcome. Though many attempts had been made to construct stabilized chairs to counteract the ship's motion, this effort had not, in his opinion, been backed up by the special knowledge which otologists could give. In the last few months an engineer friend and he had explored the possibility of constructing a chair which would eliminate for its occupant both pitch and roll, acting on the assumption that a unidirectional motion would not cause seasickness. Riding a horse did not cause it, while riding a camel produced nausea. The idea was to convert, by their chair, the motion of the camel into that of the horse, and if further experiments mature successfully he would demonstrate the chair at a meeting of the Section.

Dr. Douglas Guthrie said that a small number of children from the Shetland Isles attended the School for the Deaf in Edinburgh, and they travelled home at holiday times, often in severe storms. Yet the headmaster said that only one of the children had been noted to be susceptible to seasickness, and that child was greatly afraid of the sea, anticipating on each voyage that she would be sick. Obviously the mental attitude was of importance.

It was the unexpected movement which produced seasickness. When sailing in a yacht one became accustomed to the rhythmic rise and fall; the irregular "corkscrew" movement of a mechanically propelled vessel was more likely to cause seasickness. This fact might explain why persons liable to train sickness preferred to sit facing the engine, rather than submit to the less usual backward movement.

Mr. Sydney Scott said that though he himself did not suffer from seasickness, his experiences familiarized him with the apparent motion of the land after leaving a boat: there was no nausea with it. Perhaps this was similar to that sensation which sometimes followed fishing and wading in a fast river. Visual sensations evidently played a part; liability to seasickness diminished when the eyes were closed.

Susceptibility to seasickness differed in degree, as did labyrinthine sensitivity.

Mr. Stirk Adams' observations reminded him of a very efficient pilot with a fine war record, who declared that he was as sick as a dog on a boat and that the rotation-chair would send him almost into convulsions. Possibly this was partly due to his strenuous fighting in the air, and his nerve control might have fallen below par. Nevertheless he was able practically to throw his aeroplane about in the air without any nausea.

Another pilot mounted guard over the bier of a high officer while a constant stream of people passed by for hours. When relieved, after seeing feet moving in the same direction, he found himself giddy, and staggering to one side. This also illustrates the effect of unusual visual conditions on disorientation.

The President said that there was a psychical factor in the production of seasickness. Treatment had been only slightly alluded to by the openers. The sovereign remedy in his own (the speaker's) case, both in small sailing boats and larger vessels, was chloretone-with-caffein. For some people a combination of hyoscyamine and scopolamine was excellent and there were, of course, other useful drugs. But, above all, by lying down quietly and shutting one's eyes, one could often avert seasickness, though it might be felt almost immediately after getting up again.

Dr. Gwynne Maitland (in reply): It must be admitted that visual factors in certain exceptional cases might cause vertigo, as for instance in the quoted example of the fisherman and the river rushing by.

A better example, which illustrates what is actually taking place in the eye, is the experience of looking at a long line of passing trucks. It is found that after these have passed from the line of vision, the background, previously obscured, appears to take on movement in a direction opposite to that of the previously moving objects.

This is still better shown in the experiment of the rotating drum; when the drum is stopped the lines drawn upon it appear to move, but again, in the opposite direction to the actual movement of the drum. This illusion is due to a persistence phenomenon, called post-optic nystagmus, and may account for the occasional cases of motor-car and train sickness. The passenger susceptible to seasickness might develop sea-legs by the end of a trip, e.g. to Australia by sea. On disembarking, however, he might show clear evidence of insecurity and might even feel nausea. This, again, is an example of conditioned reflex or habit reaction. His visual sensations ashore betray him, his ocular movements anticipate movement on the solid earth, where none takes place, and his equilibrium consequently breaks down.

The drugs recommended for seasickness are innumerable, none curative, but a great many are alleviative. Drugs or apparatus which deserved examination are given a fair trial by some of the ships' surgeons, for example, by Dr. Hill of the *Aquitania*. The sedative drugs such as chloretone are the more generally useful. The use of apparatus like the swinging lamp, whose beams of light are supposed to give the eye a stable object to rest upon, or that of the swinging pillow to give

stability to the vestibule, or plugging the anodes in both ears to induce a condition of anelectrotonus with its diminution of excitability and conductivity of the 8th nerve, is of no value.

Mr. Forster (in reply) said that he had purposely omitted discussing treatment in his paper as he did not feel justified in doing so as an expert, for he had not treated seasickness in an official capacity for over twenty years.

He had himself taken chloretone in mid-Atlantic when he had been suffering from seasickness, but the headache which followed its use discouraged him from taking it again or from recommending it with enthusiasm. Chloretone, no doubt, had a sedative action on the central nervous system, but it was also known to have a local anæsthetic action on mucous membranes. Could this local action, say on the gastric mucosa, partly explain its success in some seasick patients ? He understood that it was sometimes prescribed along with caffein and aromatic chalk, as in a well-known proprietary remedy, but he had not taken this prescription himself.

He found when opening his morning letters that the manufacturing druggists appeared to be particularly interested at the moment in the pharmacology and therapeutics of drugs acting selectively on the autonomic nervous system, and some of these were being recommended for seasickness.

He had himself taken an old remedy, atropine, in the form of a pill for seasickness, but with indifferent results. If one thought out the pharmacology of an atropine pill one would appreciate that its action would be variable in such treatment. He had been much relieved that a very susceptible member of his own family had found comfort at sea in quite small doses of ammonium bromide, together with conventional doses of alcohol, in the form of gin. Bromides acted on the cerebral cortex and were simple drugs of long standing—further, we knew what to expect of them, which was certainly not the case with some other narcotics or sedatives. Female patients, however, should be warned of the effect of bromides on the skin, if taken during a lengthy voyage. Dr. John Hill, when discussing the utility of bromides in an article on seasickness, pointed out that chloral might be added because chloral was supposed to act on the thalamus.

With regard to Mr. Watson Williams' remark about older people being less susceptible to seasickness, he wondered whether this happened because, with the onset of presbyacusis, the labyrinth might also quieten down. There was, however, another side to this question which might be explained by the suggestion that whereas most children were said to be vagotonic in type it would be difficult to find a vagotonic old man.

As people grew older, however, the after-effects of seasickness lasted longer. One might reduce a tendency to seasickness by making an effort to adapt oneself to the sea. As Dr. Hill had observed, " sea-legs " would not be acquired by lying down.

CASES

Otogenic Encephalitis.—LIONEL COLLEDGE.

S. F., male, aged 15, admitted to St. George's Hospital June 20, 1937. He had had discharge from his left ear for three weeks, but before that had had no trouble with his ear. For four days he had had severe left frontal headache, and during the last three days had vomited about twenty times. On the morning of the day of admission he had had a fit, during which he was unconscious for about half an hour and passed water, but did not bite his tongue. On admission a profuse purulent discharge from the left ear was observed. The eyes were normal in every respect. The right plantar response was extensor, otherwise the reflexes were normal. No aphasia was detected. A lumbar puncture was performed and clear fluid was withdrawn, but was not kept for examination.

On exploration of the mastoid process, pus was found in the cells and in the antrum under pressure, and also a large extradural abscess in the middle fossa. The wound was kept wide open. After the operation the patient vomited twice, but had no further headache. The right plantar response continued to be extensor for about a week, but by July 2 it had become flexor. Slight signs of aphasia appeared after the operation: the patient was unable to name a person whom he knew well: he said that his tea was too weak when he meant that it was too strong, and he stumbled over simple words when asked to read aloud. All this disappeared in a few days, and the patient was discharged on July 21 as no further symptoms appeared to arouse suspicion of a brain abscess. The wound healed soundly in a few weeks.

Aural Vertigo: Effect of Injection of Adrenalin and Pituitrin.—CLEMENT FRANCIS.

V.G., female aged 27, since 1934, shortly after having measles, has had periodical attacks of tinnitus in the left ear, accompanied by nausea and vomiting. Duration up to twelve hours, during which she cannot walk or stand without support. Submucous resection of the nasal septum was performed in August 1936, to allow passage of a Eustachian catheter, after which the attacks ceased for one year, but shortly after the extraction of the right upper premolar tooth in August 1937, they recurred, and have recently been as frequent as one a week.

Hearing.—Right: Rinne positive; hearing normal. Left: Some loss of perception of high and low tones; Rinne positive.

Labyrinth reactions.—Caloric test: Responses sluggish both right and left. Turning test: Left labyrinth reaction more sluggish than right. Wassermann reaction negative.

Eye report: Fundus shows no abnormality (Mr. A. Rugg-Gunn).

X-ray report: Both labyrinths and all accessory nasal sinuses: No abnormality seen (Dr. S. Cochrane Shanks).

Blood-pressure 120/90.

There is a marked element of vasomotor disturbance associated with the attacks, which are preceded by a heavy feeling of the head and chilliness of the skin of the upper extremities, and are accompanied by profuse homolateral vasomotor rhinitis. The attacks have been brought on by stooping, and the early symptoms can be relieved for a time by vigorous rubbing of the arms, neck, and scalp. On two occasions when seen during the attacks, all symptoms have been completely relieved in a few minutes by a subcutaneous injection of 0·5 c.c. of adrenalin with pituitary extract, which it was necessary to repeat once the following day. This simple method of relieving the attacks in this case suggests a vasomotor origin, which other remedies tried (luminal, bromides, potassium iodide, ephedrine) had not influenced. The preparation used contained 0·15 unit pituitary (posterior lobe) extract and liq. adrenal. hydrochlor. B.P., 0·5 per c.c.

Section of Surgery

President—G. GREY TURNER, M.S.

[*November* 3, 1937]

DISCUSSION ON THE MANAGEMENT OF TUBERCULOUS GLANDS IN THE NECK

Mr. Claude Frankau: I propose to give you my personal views, based on the large number of cases of tuberculous cervical glands which I have observed and treated since my interest in the subject was first aroused some twenty-five years ago.

During the last fifty years there have been remarkable changes in the treatment of this condition—the pendulum swinging first one way and then the other. Prior to 1885 the general policy adopted was to allow caseating glands to burst and discharge with the inevitable result of persistent sinuses and depressed deforming scars. Surgery was restricted to curettage of sinuses and occasional "scooping-out" of superficial glands.

In 1885 Clifford Allbutt and Pridgin Teale at Leeds advocated early operative interference, with eradication of the affected glands. Excellent results were obtained in the hands of Teale and many other surgeons, among whom I must especially mention William Knight Treves of Margate who was working contemporaneously with Teale, and in more recent times my friend William Greenwood Sutcliffe, whose magnificent gland work at Margate is well known and still continues. On the whole, however, this treatment was not uniformly satisfactory, the want of complete success being in part due to a failure to understand the pathology of the condition and in part to a neglect of prophylaxis and after-care.

Some thirty years ago the pendulum swung the other way; operations were thought to be unnecessary and inadvisable, and treatment by hygienic methods in sanatoria—with simple aspiration of abscesses and the use of tuberculin—was strongly advocated. This line of treatment was based on a better knowledge of the pathology of the condition but had its disadvantages, firstly because it passed into the hands of men who were essentially unsurgical, and secondly, from the economic point of view, owing to the lengthy treatment required. In the last fifteen years the tendency has been to combine surgery with this latter method, special stress being laid on the treatment of the paths of infection and on after-care. The results now are, I think, definitely better, and a cure is more quickly obtained than was the case formerly.

To obtain a proper perspective a few points on the pathology and paths of infection are needed: The infection is bovine in 90% of all cases with milk as the infecting agent in nearly every case.

The actual paths of infection fall into three main groups.

(*a*) *Through the nasopharynx*, especially the tonsils, in which tubercle bacilli can be seen in sections after removal in some instances. The glands first affected are those situated behind the angle of the jaw, then a superficial set running down the anterior border of the sternomastoid, and finally a deep set surrounding the carotid sheath.

(*b*) *Through the intestinal tract.*—Mesenteric glands are first affected; a spread upwards then occurs along the thoracic and right lymphatic ducts to the glands in

the posterior triangles at the base of the neck, thence to a superficial set along the posterior border of the sternomastoid and a deep set around the carotid sheath.

(*c*) *The mediastinal type.*—The initial infection is in the mediastinal glands, either primary in glands or secondary to a pulmonary infection ; this type is the only one in which pulmonary tuberculosis is at all commonly present. The glands involved are at the base of the neck in the posterior triangles and in the space of Burns between the two sternomastoid muscles, forming a kind of collar infection. Whereas the first two types mainly occur in young patients, the third group is more common in the middle-aged or old, and may be extremely virulent in such patients.

All these types may occur spontaneously in apparently healthy persons ; not infrequently, however, the initial invasion or a flare-up of existing infected glands follows a febrile attack or a tonsillar infection.

Of the differential diagnosis I need say little here, as in most cases the diagnosis, after careful observation, is relatively easy. Every honest surgeon, however, will admit of having mistaken a branchial cyst for a breaking-down gland, and vice versa, and of having failed to diagnose lymphadenoma until a gland has been removed.

From the point of view of treatment the cases fall into five groups : Those in which

(1) There is a single enlarged gland or a small group of glands with no sign of caseation or periadenitis.

(2) A gland is definitely caseous or, from its sudden increase in size, caseation is suspected.

(3) The chief feature is a subcutaneous cold abscess of the " collar-stud " variety, where the caseous material has broken through the capsule of the gland and then through the deep fascia.

(4) There is diffuse bilateral enlargement of all groups of glands—the enlargement being not gross and no marked periadenitis being present.

(5) There is the massive diffuse type of enlargement, the glands being fused into fixed masses.

In Group 1 non-operative treatment is the line to adopt at first. As in all types of case, it is essential to eliminate foci of infection in the mouth and nasopharynx as far as possible, always, however, remembering that tonsillectomy, if carried out, may be followed by a flare-up of the affected glands owing to superadded sepsis. Put the patient in the best hygienic surroundings with the maximum amount of sun and fresh air. Forbid any violent exercise, in fact the more rest the better. Give a liberal diet with extra fatty foods. Of drugs, I am old-fashioned enough to think that cod-liver oil with malt holds pride of place with, in addition, syrup of iodide of iron in moderate doses. Watch the case carefully and continue palliative treatment only if there is a steady diminution in the size of the glands. After from six to eight weeks if there is no improvement—or earlier, if there is any increase in the size of the glands or evidence of caseation—operation is advisable.

In Group 2 in which caseation is present or is suspected, early operation is essential before complete breaking-down of the gland occurs. This allows the removal of the glands without rupturing them and gives, with care, a very insignificant scar. The incision must be carefully planned to run in a natural crease of the neck, as far as possible, so as to give the best cosmetic result. My practice is to remove the grossly-infected glands and the smaller glands in close relationship to them. It is notorious that at operation many more enlarged glands are found than had been suspected, and considerable experience is necessary to know where to stop. It is hardly necessary to remark that an accurate knowledge of the anatomy of the neck is essential, so as to avoid damage to important structures, and that invariably, sooner or later, the internal jugular vein comes into view during the operation.

In Group 3, in which there is a subcutaneous cold abscess, it must be remembered that this is a secondary and superficial manifestation of extensive disease deep to

deep fascia. This type of case has been commonly treated by aspiration, but in my opinion this is an unsatisfactory method and only palliative. Aspiration should be reserved for cases in which the skin is reddened, so as to save further skin infection and to allow of an easier operation, with a better cosmetic result, at a later date. I advise an incision as near to the abscess as possible, through comparatively healthy skin, evacuation of the caseous material, and thorough cleansing of the cavity. A search is then made for the perforation in the deep fascia; this is enlarged carefully and in the majority of cases the affected gland can be identified and dissected out. Admittedly this may be difficult, especially if there is much matting around the gland, but a line of cleavage between the gland capsule and surrounding tissues can usually be found.

After any gland operation, and particularly in this type of case, careful after-treatment is essential. Patients must never be hurried out of hospital or nursing home; absolute solid healing of the wound is desirable before they are allowed up. Subsequently, six weeks—or longer if possible—by the sea, or in the open air in the country, completes the cure and minimizes the risk of further infection.

In Group 4, in which multiple small glands are present, no operation is indicated unless caseation should occur in any individual gland, and that gland alone should then be removed. The treatment should be on the general lines indicated in Group 1—with this addition—that in this type, and this type alone, have I seen good results from irradiation with X-rays.

In Group 5 in which there is massive glandular enlargement with much periadenitis, a condition which nowadays is fortunately becoming rare, operations, apart from the evacuation of caseous material, would involve such a heroic proceeding that they should be avoided. With prolonged general treatment and absolute rest in bed, in the open air, it is astonishing how many of these cases subside sufficiently to allow of a relatively easy operative removal of the glands.

Of tuberculin in these cases I have no good word to say; at one time its use was strongly advocated in various dosages, but the only effect obtainable from its use is a rapid breaking down of the affected glands. The protagonists of aspiration at one time advised tuberculin for this very purpose, which seems to me to have no justification.

Irradiation has its place, as I have indicated, but although it can and does help in minor diffuse enlargements, it cannot have any possible effect on glands which are full of caseous deposits.

To sum up: Operation is advisable—(1) For single glands or small groups of glands which do not subside under prolonged and adequate general treatment or in which signs of caseation or periadenitis develop. (2) For glands in which caseation has occurred. (3) For "collar-stud" abscess.

Operation, apart from the evacuation of caseous material, is to be avoided: (1) In massive infections. (2) In diffuse involvement of many small glands.

Avoid heroic operations involving division of the sternomastoid, &c.

Remember that after the most satisfactory operation prolonged after-treatment is necessary.

Mr. Gordon Pugh, describing his experience at Queen Mary's Hospital, Carshalton, said it had been realized by the controlling authority that the development of any tuberculous lesion was evidence of lack of resistance to this infection, and that to raise the resistance adequately would require healthy surroundings and good food during a prolonged period. All the cases of tuberculous adenitis admitted had already had treatment elsewhere, and the majority of the patients had had their teeth and tonsils attended to, while only in a relatively small number was the skin uninjured by scar or sinus. Notwithstanding this, only one child was received with spinal-accessory-nerve paralysis. Previous to the Great War patients with

recurrences following excision were more common than those in whom abscesses had been dealt with as they formed, and whose glands had not been removed. After the War this position was reversed. None of the children admitted had previously had radium treatment, very few had had tuberculin, and only one had been given X-rays. At Carshalton, life in the open air, attention to tonsils and teeth, heliotherapy, light treatment, good food, cod-liver oil, and so on, had always been available, and most patients benefited greatly by this constitutional treatment. Neither tuberculin nor X-ray treatment was used. Before 1920 the local treatment had consisted in aspirating or opening abscesses, curetting ulcers and sinuses that were long in healing, and excising disfiguring scars. If this treatment proved insufficient the glands were excised. In 1920 the hospital purchased a half-strength radium applicator with an area of 4 sq. cm.—the smallest suitable for treating glands. The number of cases in which excision became necessary fell at once ; indeed, during the five years, 1923–27, the operation of excision was not once performed. Out of 1,048 consecutive cases, half of which were admitted previous to and half subsequent to the date of the purchase of the radium, excision was performed in 20% of the former and only 5% of the latter. Practically all the excisions of recent years had been performed in cases in which the patient was admitted with sinuses which did not heal readily. The radium also proved effective in dealing with keloid scars. The technique used was that described by E. S. Molyneux in the *British Medical Journal*, 1919 (ii), 705, modified in detail to accord with his later practice. The applicator was screened by a silver plate, 1 mm. thick, and several layers of paper, to filter off the β and secondary rays respectively, and the whole was covered with gutta-percha tissue, tightly tied with thread behind the applicator. The areas to be treated were charted and the radium was applied to each in turn for four hours at a time once a week. The applications generally numbered from twenty to thirty-five ; if more than forty-five were given there was risk of freckling and telangiectasis being produced, undermined skin and thin scars requiring particular care in this respect. Usually no change in the size of the glands was noticed until several applications had been made : then they gradually became smaller, the less affected ones disappearing and the however many further applications were made. Two of these nodules were more advanced shrinking to a firm fibrous nodule, which refused to become smaller excised, and were found to consist of a thick fibrous capsule enclosing a tough material of wash-leather appearance, no gland tissue being evident macroscopically. Dr. J. C. Mottram of the Radium Institute (*Lancet*, 1926 (i), 1118) stated that the structural changes in tuberculous glands following radium treatment were an early disappearance of the lymphocytes and a great increase of fibrous tissue, in which giant cells and tubercle bacilli might be present, so that the whole gland, shrunken from loss of lymphocytes and other cells, came to consist of narrow spaces lined by endothelial cells running through fibrous tissue. At the Radium Institute applicators of the same strength, but of much greater area, were employed, and an approved practice was to give six hours' irradiation daily on five consecutive days, the treatment being repeated after an interval of two months. Radium had been used for well over 300 patients at Carshalton, each with several masses of glands. The benefit appeared to be lasting in most cases, for only two patients who had received radium treatment had been readmitted—one with an abscess in the neighbourhood of a gland which had been so treated, the other with an enlarged gland in another part of the neck.

No advocate of either operative or conservative treatment, however, could feel fully satisfied with the present average result, and the reason appeared to be that effective measures were not adopted early enough. Sometimes the family doctor hesitated to diagnose tuberculosis, delay might occur through waiting to see the effect of the removal of tonsils and adenoids, and the parents often procrastinated in sanctioning operation. In London the most satisfactory feature of the recent

past had been a remarkable reduction in the incidence and severity of tuberculous adenitis, due doubtless to the pasteurization of milk and the attention given to teeth and tonsils at the elementary schools. With regard to the future, he was satisfied that a great improvement would follow the use of radium in the earlier stages, without waiting till extension of the disease or softening of a gland had made both diagnosis and skin disfigurement certain. The cost of radium element had fallen since 1920 from £32 per mgm. to £4 10s.; an applicator like that used at Carshalton now cost under £50, and this would suffice when expense was a consideration. The technique of its use was simple and safe, and caused little upset in the routine of the life of a child. He ventured to suggest that no tuberculosis dispensary, sanatorium, or hospital dealing with these cases, should be without at least one applicator, and that every tuberculosis authority should be in a position to lend one to a family doctor who under these circumstances would probably not hesitate to seek early the co-operation of the tuberculosis officer.

Dr. B. W. Windeyer said he proposed to give an analysis of 203 cases treated by radiotherapy at the Middlesex Hospital from 1931–37, dividing them into three groups, according to the method of treatment employed: (*a*) Surgery with subsequent radiotherapy, (*b*) X-rays, and (*c*) radium.

TABLE I.

	Surgery and radiotherapy	X-rays	Radium	Total
Total cases	28	26	149	203
Good	15	12	90	117
Improved	4	3	36	43
Unimproved	7	7	11	25
Lost	2	4	12	18

Percentage	Radium	Total
Good	60·4%	57·6%
Improved	24·1%	21·1%
Unimproved	7·3%	12·3%
Lost	8·0%	8·8%

Good and improved results (added together)

Radium alone	84·5%
Total treated	78·7%
With histological confirmation of diagnosis	76%

GROUP A—SURGERY AND RADIOTHERAPY

The majority of cases had had fluctuant glands which had been dissected or scraped out, and subsequent radiotherapy had apparently been given for one of three reasons: (*a*) As a prophylactic measure to prevent recurrence. (*b*) As an auxiliary treatment in cases in which glands still remained after excision. (*c*) To improve the resultant scar.

In all but two or three the radiotherapeutic agent used had been X-rays. These two or three cases had been given surface application of radium.

The results of this rather mixed group showed that out of 28 cases treated (Table I) good results followed in 15 cases, 4 were improved, and 7 were not improved. As the number of cases was small and the conditions very diverse, he had not thought it worth while to analyse this group further.

GROUP B—X-RAY

Two techniques had been used in the treatment of these cases. In the earlier period they were treated with 150 kv., 3 mm. aluminium filter, and a focal skin distance of 23 cm. The dose given was one-sixth of an erythema dose, which, so far as could be judged, was between 50 and 80 r. Treatments were given at weekly intervals, the average total treatment consisting of six such doses, although sometimes as many

as twelve were given. During the last three years some cases had been treated at 190 kv. with a filter of 1 mm. copper plus 1 mm. aluminium, with 50 cm. focal skin distance, a dose of 100 r being given at weekly intervals for six weeks.

TABLE II.—X-RAY CASES—TOTAL 26.

	Old technique	New technique
Good	6	5
Improved	2	1
Unimproved	6	1
Lost	2	2
Total	16	9

One case with good result was treated by a combination of the two techniques.

Sixteen cases were treated by the old technique, and nine by the new (results in Table II). It would appear that the results of the higher kv. technique were better than those obtained by the old method, but the numbers were too small to draw any definite conclusion.

GROUP C—RADIUM

The cases were treated as out-patients by surface applications of radium on applicators made of Columbia paste 1·5 cm. thick. The radium had a filtration of 0·5 or 1 mm. of platinum. The amount of radium varied between 45 and 200 mgm. The length of the period of treatment had been about ten hours, divided over two days at the first treatment, but generally a shorter period at subsequent treatments. The dose given at each treatment varied between 250 and 800 r. This had been given at intervals of a month or six weeks, and continued as long as was thought necessary. In some cases two or three treatments had been sufficient, but in others as many as eleven had been given and good results obtained. In no case was telangiectasis or damage of the skin observed. The results appear in Table I.

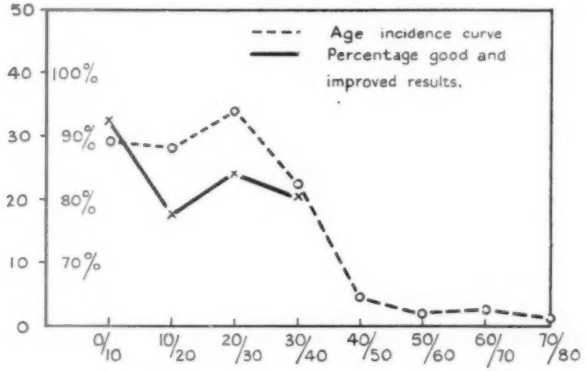
Radiotherapy in tuberculous glands of the neck has attained its results as an adjunct to constitutional treatment, which must remain the most important factor of all. It must be clearly understood that no attempt is made to destroy the tuberculous process directly by radiation. The principles underlying its application are entirely different from those employed in the radiotherapeutic treatment of cancer. The object is to cause a slight local aseptic inflammatory reaction which will aid the general defensive reaction of the body, and later to increase the normal fibrosis of repair. To do this very small doses of X-rays or radium must be given. These must be such that, clinically, there is no sign of erythema or visible reaction from the treatment. If larger doses are given, considerable harm may be done, and the normal tissues will be damaged. The patient's general condition will deteriorate, and instead of any improvement taking place in the defence mechanism, this will be temporarily or permanently destroyed. It is therefore necessary, in the successful treatment of the patient with tuberculous glands, by radiotherapy, to undertake also all measures which will promote the patient's general health. Ideally, I presume, this should be brought about by sanatorium methods, and if such could be carried out one would expect these results to be better, but the great majority of cases in this series have been patients who have been unable to go for sanatorium treatment. They have almost all been treated as out-patients and in many cases it has been necessary for them to carry on with their normal occupation. Every effort has been made to obtain for them as much fresh air, suitable food, and rest, as possible.

Septic foci, such as tonsils and bad teeth, must be removed, as—although the results of removal of tonsils and teeth, by themselves, are disappointing with regard to the subsidence of tuberculous glands—it is nevertheless necessary that these sources of infection should be eliminated before success can be obtained with radiotherapy. Similarly it is necessary to aspirate and remove all breakdown products from the

glands ; in this series a large proportion have had fluctuant glands or abscesses, and repeated aspirations have been undertaken during treatment.

I have attempted to divide this series into different clinical types : (1) Small discrete multiple glands ; (2) large fleshy firm glands ; (3) fluctuant glands ; and (4) collar-stud abscesses. I do not, however, think that any real purpose can be served by this step as it is almost impossible to divide them satisfactorily. I think the fluctuant gland cannot clinically be diagnosed differentially from the large fleshy gland, since on section of the former there will very frequently be found small caseous areas. I believe it is largely for this reason that I cannot find any sufficiently marked difference in the results obtained in the different clinical types, though I have definitely formed the opinion that the multiple small discrete glands do not give such a good response to this form of therapy as do the large and fluctuant glands and the definite abscess types. In some cases they have disappeared entirely, but in many, although the glands have become smaller, they have remained definitely palpable, and I think they are liable to recrudescence. These are the types which have largely come into the group of " improved " cases. The large fleshy type of gland may disappear more

TABLE II'.



rapidly, but one frequently finds cases in which there is a large fleshy gland and multiple small discrete glands as well, and in these the result obtained may be the disappearance of the large gland, but only a minor diminution in the size of the remainder. The fluctuant gland and the collar-stud abscess need repeated aspiration, but they frequently heal completely with no underlying induration and the scar after radiotherapy is usually soft and not adherent. Sometimes, however, they may heal but leave a small calcareous nodule remaining deep in the tissues. After an indefinite period, maybe one or two years, this may light up again into an abscess, the calcareous nodule discharges, and the whole area finally heals up. There has not been any difference in the method of radiotherapy used for the different types ; fluctuation or abscess-formation has been no contra-indication.

The condition seen in young children, of generalized tuberculosis with enlargement of glands in the neck, axillæ, groins, and abdomen, does not, I think, come into the province of radiotherapeutic treatment.

In the 149 cases treated by radium I have analysed the age incidence and also the percentage in the various decades which show good and improved results (Table III).

The results in the radium group show an improvement over those obtained in

the X-ray group. Actually this latter group is too small for any definite conclusions to be drawn. Personally, however, I consider that this is a question of technique, and that just as good results can be obtained with X-rays as with radium ; I hope this is the case. Surface application of radium has the considerable disadvantage that in the construction of large moulded applicators it is necessary for the personnel of the department to handle large quantities of radium, with consequent possible danger to their health ; especially is this so in large and busy clinics.

The figures in these cases show, I think, that radiotherapy has a definite place in the treatment of tuberculous glands as an aid to constitutional treatment. It must be used carefully as considerable harm can be done by an injudicious selection of cases, or excessive doses. In this series there have been two cases in which pulmonary tuberculosis has become manifest shortly after radiotherapy for glands has been given, and in one case the patient almost immediately became very ill and died from tuberculous pericarditis. In spite of these instances, this series has been carefully selected for radiotherapy. Many other cases have been sent for surgical treatment and others for sanatorium treatment. The cases treated were those in which it seemed justifiable to give radiotherapy, and those in which it seemed desirable to give treatment as out-patients, as the patients could not or would not go to a sanatorium. Latterly an X-ray examination of the thorax in adult cases and a test of the sputum have been made as a routine before they are subjected to radiotherapy.

It may be said that the length of time—six months to a year—over which these patients must be treated is a great disadvantage, as opposed to the more rapid results obtained by surgery, but there is no doubt that the cosmetic results of radiotherapy are immeasurably superior to those obtained by successful surgical treatment.

I believe that, quite apart from the therapeutic value of radiotherapy, it has a place in those cases dealt with successfully by surgery, in the treatment of the resultant scar. In almost every case, if radiotherapy is not too long withheld, the scar can be made soft and supple.

Finally, some of the cases which have failed to respond to radiotherapy have been sent for surgical excision. This procedure has not been made more difficult by the previous radiotherapy and, in fact, should be made less difficult, by the reduction of periadenitis.

Mr. Philip Turner said he had noticed that though recently enlarged glands could be made to shrink by treatment with X-rays and radium, it was admitted that it was not uncommon for small, palpable, hard nodules to persist. Another disadvantage of this treatment was its duration, as it might have to be carried out for from six to twelve months.

He did not favour aspiration of breaking-down glands, but preferred to make a small incision and to thoroughly empty and curette the cavity with subsequent suture of the wound.

The tonsils, if diseased or enlarged, should not be removed at the same time, on account of the probability of secondary infection. He had treated a number of cases with hypertrophied tonsils and tuberculous glands by removal of the glands followed by injection of the tonsils with " ethidol ", a solution of ethyl iodoricinoleate. In many cases the tonsils had shrunk up and had required no further treatment.

There was one type of case that had not been mentioned, namely, the old-standing case with several sinuses burrowing deeply in the neck and inter-communicating, with extensive matting and induration due to periadenitis. Though formerly these were by no means uncommon they were, fortunately, very rarely seen at the present time. He had successfully treated some of these cases by curetting as thoroughly as possible and then by diathermy, using a small bullet-nosed electrode, which was applied to the sinuses from their external opening to the deeper recesses which had been opened up by the curette.

Mr. M. F. Nicholls said that in listening to the discussion he had been struck by his profound ignorance of the subject, in spite of the fact that he had been on the staff of a children's hospital for five years or more. He could not help feeling that the severe cases described by some of the other speakers were not now seen, and that owing to preventative treatment, and possibly to some constitutional change in the health of the nation, the tuberculous infection of the glands of the neck was now more mild in its manifestations than formerly.

He suggested that such cases would now do well under any form of careful treatment, whether surgical or radiological, and he felt that a proper control of the results of radiotherapy would be a series of similar cases in which nothing but general hygienic treatment was undertaken.

Mr. Charles Donald said that the proper procedure in these cases varied with the rapidity or slowness of the glandular involvement, which, in turn, depended on the virulence of the infection. In rapidly spreading cases he advocated conservative procedures, since operation was not unlikely to be followed by the occurrence of infection in glands not large enough to be detected at the dissection. Aspiration by needle and syringe was frequently a disappointing procedure in abscess cases and he did not hesitate, especially when skin was becoming involved, to go back to the old practice of making a tiny incision in a crease of the neck, expressing the pus gently, then curetting out gently, through the hole in the deep fascia, the more solid material. This procedure frequently obviated unsightly scars, and dissection, if required, could be carried out later. Immobilization of the head and neck in these more acute cases was of definite value.

When, however, the progress of glandular enlargement was slow or hung fire, he was in favour of dissection, and this could be done without leaving obvious traces by planned incisions and careful suturing.

Professor Grey Turner said that at the outset of his career it was the custom of the surgeons in Newcastle-upon-Tyne to operate on all the examples of tuberculous glands of the neck which came under their notice, and he was accustomed to see the most beautiful dissections carried out in these cases, but he soon learned that the results were often disappointing.

After some years he was able to convince himself that the varying results were due to the fact that all the cases of tuberculous glands were, so to speak, lumped together, and the same operative treatment was meted out to all. As the result of clinical observation, post-mortem investigation, and anatomical study, combined with bacteriological examination of material from the nasopharynx, he had long ago reached the conclusion that most cases of tuberculous glands fell into two great groups. First, those in which the portal of infection was in the tonsils or nasopharynx, and secondly those in which the portal could be found in the mediastinum or in the mesentery. In the former group the portal of invasion and the consequences of that invasion were closely related, and the disease was usually localized to the tonsillar group of glands, or at least the upper cervical group, although those groups on both sides of the neck might be involved. He was quite sure that infection by this portal was only likely to occur in the earlier years of life, probably within the first two, but he had abundant evidence to show that the bacilli might lie dormant in the glands until many years later, when, with some particular lowered resistance, they were prompted to become active again. In this nasopharyngeal group he was satisfied that thorough operative removal was the method of treatment, and far superior to any other, but it was necessary that interference should be thorough and should aim at clearing out not only one or more of the invaded glands, but the whole group of glands in the upper cervical region, and, if necessary, on both sides. He knew perfectly well that some of these cases had been cured as the result of other

methods of treatment, but it was surprising how often he had been asked to deal with cases that had been " cured " many times by other methods. The infection might remain active and give a great deal of trouble for several years, and he had often had to deal with cases of old-standing sinuses, abscesses, and recurring periadenitis, which had not been influenced by other methods of treatment.

In the other group of cases in which the portal of infection was in the trunk, the problem was quite a different one. In these cases the patients were usually older before the glands became involved; quite often this occurred at the beginning of adolescence. The fact that the neck glands were involved was evidence of some breakdown in resistance, and if to that was super-added the acute lowering of resistance associated with an operation, it was almost certain to be followed by an outbreak of activity in some other area. In this group the treatment was general, and directed especially to raise the natural resistance of the individual. The accessible groups of glands might, of course, be influenced by various forms of light treatment, irradiation, vaccines, &c., but there might be a stage in which surgical interference was necessary. In contra-distinction, however, to the treatment of the pharyngeal group, operation was not the main method of management in this group, but was only a surgical incident, important though it might be.

Mr. Gordon Pugh (in reply to two objections to radium treatment which had been raised in the discussion, namely, the length of the course, and the fact that living tubercle bacilli were left locked up in the fibrosed glands) said that the treatment could readily be fitted into a normal life, and its length was rather an advantage than otherwise, as it encouraged an adequate period of constitutional treatment. The imprisonment of the bacilli appeared to be generally a secure one, judging from the rarity of recurrence, whereas even radical excision could not ensure the eviction of all the bacilli, since these were to be found in glands not obviously enlarged and, as a result, recurrence after operation was relatively common.

Clinical Section

President—B. T. PARSONS-SMITH, M.D.

[*November* 12, 1937]

Two Cases of Chronic Œdema of Legs with High Blood-pressure.—F. PARKES WEBER, M.D., and A. SCHLÜTER, M.D.

(I) C. H., male, aged 61, has had chronic œdema of the legs, with tendency to " bag " at the ankles (see fig.), since about 1929.

No visible œdema of thighs or trunk. Brachial blood-pressure : 200/130 mm. Hg ; otherwise no obvious sign of disease. The patient is of good general nutrition, not

Case I.

obese, feels well, and lives a fairly active life. Electrocardiogram normal. Urine free from albumin and sugar ; nothing abnormal by microscopic examination. Blood-Wassermann reaction negative. The œdema is diminished by rest in bed, but does

not entirely disappear. He has had digitalis (elsewhere) for the œdema, but without result. Nothing special in regard to diet; no alcohol. In 1928 a posterior gastro-jejunostomy was performed for a juxta-pyloric gastric ulcer. He had considerable mental worry of long duration some time ago.

It was suggested that the diminished resistance to postural (orthostatic) œdema in this case might be the manifestation of a senile degenerative process analogous to degenerative processes limited to special tissues or organs of the body.

POSTSCRIPT (November 19, 1937).—Blood-plasma total protein estimated at 4·4%.

(II) Mrs. E. A., aged 51, has symmetrical moderate œdema of the feet and lower part of the legs. Brachial blood-pressure: 200/125 to 225/135 mm. Hg. The patient, who is of average general nutrition, has been deaf for the last twelve years (otosclerosis) and (lately) has had some chronic rheumatoid trouble in the knees. Urine free from albumin and sugar; nothing abnormal found by microscopic examination. Blood-Wassermann reaction negative. Electrocardiogram shows some left-sided preponderance. Otherwise nothing abnormal has been found. The œdema is stated to disappear with rest in bed. Patient says that the œdema commenced at about the age of 48 years, but a sister, Mrs. A. C., aged 46, who has had variable œdema of the feet and ankles since the age of 14 years, and whose brachial blood-pressure is only 120/75 mm. Hg, says that patient (Mrs. E. A.) has really had the œdema from girlhood. These two sisters are of a family of 16 sibs, of whom 5 females and 4 males are still living. Mrs. A. C. thinks that all the sisters, but none of the brothers, have had more or less œdema of this kind. In Mrs. A. C. the œdema was temporarily increased during her five pregnancies (four of her children are said to be living and normal).

The œdema in Mrs. E. A. and her sisters seems therefore to be really of the Nonne-Milroy-Meige class, though of slight degree.

Discussion.—The PRESIDENT suggested that the dependent œdema observed occasionally in cases of hypertensive heart disease was in all probability due to local errors in the functional efficiency of the capillaries possibly also of the lymphatics; raised venous pressure might be one of the underlying factors as also diminution in the protein content of the plasma; he advised that the venous pressure and the plasma protein should be estimated in both cases.

Dr. RICHARD ELLIS raised the question whether cases of this type were comparable to the not-infrequent examples of œdema seen in young infants, in which neither renal nor cardiac disease was responsible. In one case at present under observation, the œdema had disappeared and reappeared over a period of weeks, in one of healthy twins, whilst in another pair of healthy twins (both over 5 lb. in weight) the œdema varied greatly in intensity at different times. He suggested that tight binders and abdominal belts might possibly accentuate a tendency to œdema in patients in whom there was a congenital weakness of capillary resistance. It would also be interesting to know whether these infants again showed œdema when senile changes occurred in later life; unfortunately a patient aged 60 was hardly likely to know if he had had œdema of his legs during the first fortnight after birth.

A Patient Sixteen Years after an Operation for Acute Diverticulitis.—PHILIP TURNER, M.S.

Mrs. M. P., aged 56, was admitted to a medical ward in St. Mary Abbots Hospital in September 1937, under the care of Dr. J. W. Osborne (who investigated the present condition and kindly brought the case to my notice), on account of weakness and continued slight pyrexia following an attack of "gastric influenza".

History.—She had been seen by me on June 20, 1921, in consultation with Dr. W. I. Robertson, of Dulwich, because of acute abdominal trouble, of which she gave

the following history : She had always been strong and well and had had no previous attacks of abdominal pain. During the first week of that month she had begun to have vague abdominal pain and discomfort ; this was not severe, and she continued to get about. On June 17 the pain became more severe and settled in the left iliac fossa ; it was continuous and throbbing in character. She had nausea but no actual vomiting. The bowels had not acted well since the onset of pain. For three days there had been slight pyrexia (99–100·4). Menstruation was normal. *On examination.*—Rigidity and tenderness in lower left quadrant ; a large, fixed, very tender lump occupied the left iliac fossa. No irritability of bladder ; urine normal. Nothing abnormal found on rectal examination. *Operation* (June 21, 1921).—The abdomen was opened by a vertical incision over the lump, which was not adherent to the abdominal wall. The mass was elastic, smooth, intensely congested, fixed to the iliac fossa, and its maximum diameter was about 3 in. Normal colon could be seen entering it above, while below a short length of colon could be felt between it and the pelvi-rectal junction. Numerous diverticula, some of which contained fæcal concretions, could be seen and felt. At one spot there was a grey area about an inch in diameter where softening had occurred. This was incised and about half an ounce of pus was evacuated. The abscess cavity was drained. The patient did well after the operation. Pain and tenderness subsided and the temperature became normal. A fæcal fistula developed but this closed spontaneously, and in about a month the wound had completely healed. A few weeks later an X-ray investigation was made after an opaque enema ; this showed many diverticula in the sigmoid and right round the transverse colon. She was discharged apparently quite well and was lost sight of until a month ago.

After-history.—Since 1921 abdominal symptoms have been very slight. There have been occasional attacks of discomfort rather than pain. Nine years ago she had a " chill " with some abdominal pain : the motions then contained mucus, but no blood. This and the recent attack of " abdominal influenza " are the only definite attacks, and neither of these was anything like so severe as the original illness in 1921. In 1930, while in New Zealand, she had an operation on the thyroid which had enlarged and had affected her heart.

Present condition.—When admitted to St. Mary Abbots Hospital, there was no abdominal pain or tenderness and nothing abnormal could be found on examination. She had one or two fainting attacks which led to an investigation of the heart, and a cardiogram showed auricular fibrillation. An X-ray examination after an opaque enema showed many diverticula, the condition apparently being much the same as that found sixteen years ago.

Pick's Disease.—N. M. JACOBY, M.R.C.P. (introduced by Dr. R. W. B. ELLIS).

A. W., male, aged 12½, the elder of two children of a healthy family.

Previous history.—Measles and chicken-pox, uncomplicated, in infancy. Acute rheumatism at age of 5 years ; in bed eight weeks ; heart not affected. Acute rheumatism again at age of 10. Developed acute pericarditis ; in bed ten weeks ; absent from school six months.

Present history.—Has been well since the attack of pericarditis but the abdomen has enlarged during the past 3–6 months. Has had slight dyspnœa on moderate exertion.

On examination.—Fairly well-developed boy ; weight 70 lb. Prominent abdomen, circumference 24½ in. ; pulse-rate 80–100. Apex beat 1 in. outside nipple line. Dullness to right of sternum about 1 in. Systolic retraction of 5th and 6th ribs anteriorly. Broadbent's sign negative. Apical systolic murmur ; faint diastolic. To-and-fro murmur in aortic area. External jugular veins congested. No arterial pulsation. Blood-pressure 110/70. Liver enlarged below umbilicus ; firm, not tender ;

not pulsating. Spleen palpable. Free fluid in abdomen, no œdema elsewhere. No clubbing.

Skiagram: Heart enlarged; mediastinum of unusual breadth (fig. 1).

Orthodiagraph (Dr. Lindsay Locke): Heart, 13·5 cm.; chest, 21·3 cm.

Electrocardiograph (Dr. Maurice Campbell): Inverted T2 and T3 and some lengthening of the PR interval (fig. 2).

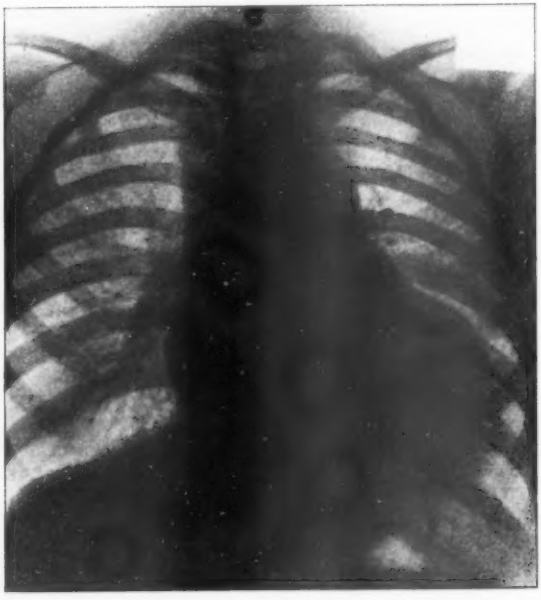


FIG. 1.—Showing cardiac enlargement and broad mediastinum.

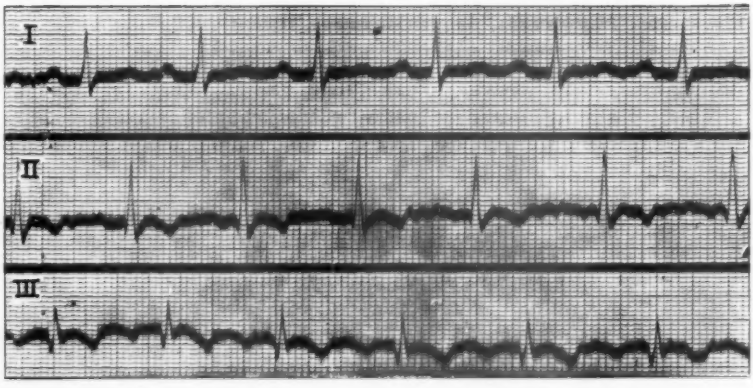


FIG. 2.—Electrocardiograph showing prolonged PR interval and inverted T2 and T3.

Discussion.—The PRESIDENT said he regarded the case as one of rheumatic carditis with enlargement of the heart, aortic incompetence, and probably undeveloped mitral stenosis. In spite of the history of pericarditis, the hepatic enlargement, the jugular stasis, &c., he was unable to reconcile the condition with Paul White's classical description of Pick's Disease, in the development of which incidentally, pneumonia, tuberculosis and other infections were regarded as ætiological rather than rheumatism. He (the speaker) thought that the cardiac enlargement and the vigorous præcordial pulsation contra-indicated a diagnosis of Pick's disease as did also the facts that the pulse pressure (40 mm.) was within normal limits and that there had been no record of pulsus paradoxus; on the evidence so far available he did not see any indication for operative interference but he advised that the case should be investigated radiologically at regular intervals in the future to determine the pulsatile capacity of the heart chambers, the degree of the venous stasis, the extent of the diaphragmatic excursion and the possible presence of calcareous deposits in the pericardium.

Mr. J. E. H. ROBERTS said he thought this child had an adherent pericardium, and that the symptoms he was suffering from were due to that, and not to any endocardial disease. He would undoubtedly die within the next few years, and unless it was considered that there was a progressive valvular disease the adherent pericardium should be removed.

He had shown at a meeting of the Section in 1935 a case of a boy aged 13 in which he had removed the calcified pericardium and in which the ascites had progressed to a further degree, so that after repeated aspirations 14½ pints had accumulated in three weeks. The boy remained completely free from symptoms after more than two and a half years, played football, and was earning his living.

In Dr. Jacoby's case he believed the operation, if done at this stage, would be less difficult than usual and would be very likely to restore the boy to health.

Spondylitis of von Bechterew.—ERNEST FLETCHER, M.D. (shown by Dr. Z. E. ZUCKERMAN).

N. B., female, aged 43, gives a history of "pneumonia" two years ago, since when she has had pain over the thoracic spine, radiating round the chest, and also in the neck—which appears to become fixed on some occasions—in the shoulders, elbows, wrists, hips, knees, and ankles.

On examination.—General condition good. Heart and lungs normal; blood-pressure 107/64; abdomen has three surgical scars; liver and spleen not palpable. Spine: Cervical movements restricted; thoracic movements normal but painful; vertebræ tender. No focus of infection discovered. Blood sedimentation rate: 2·5 mm. at the hour. Skiagram of spine shows early calcification of anterior common ligament.

Dr. WARREN CROWE said that there was radiographic evidence of spondylitis osteo-arthritis. This was not, he believed, ever seen with the spondylitis of the adolescent (spondylose rhizomélique). There were three varieties of spondylitis adolescens: The syndrome of von Bechterew, which began as a rule in the cervical spine, the Marie-Strümpell type which attacked the lumbar region, and lastly, worst of all, that form of the disease which began in the hip-joints. All three forms were linked together and shown to be one disease by the pre-spondylitic stage of a symptomless bilateral sacro-ilitis. In the case under consideration, the diagnosis could be settled definitely by a skiagram of the sacro-iliac joints.

Cataract in a Youth, with Chronic Renal Disease.—ALICE STEWART, M.D. (introduced by F. PARKES WEBER, M.D.).

S. K., aged 17, male of small build, attended the Eye Department, complaining of mistiness of vision. He was found to have bilateral, diffuse, incomplete cataract of metabolic type (Ida Mann) and was admitted for investigation.

Further examination revealed a dry skin, with furunculosis, albuminuria, a high blood urea and low blood calcium, no cardiac enlargement, and a normal blood-pressure. Urine: Specific gravity 1010; neutral reaction; "heavy cloud" albumin; no sugar; nothing abnormal by microscopic examination. Urine in twenty-four hours measured 40 to 60 oz. with a fluid intake of 50 oz.

Blood-count: Erythros. 3,780,000; Hb. 74%; C.I. 1·0; leucos. 9,800.

Blood urea 316 mgm. %; serum calcium 7·5 mgm. %; inorganic phosphorus 6·1 mgm. %. Brachial blood-pressure 110/80. Nothing abnormal felt by abdominal palpation. Blood-Wassermann reaction, negative.

Skiagrams of skull showed dense shadowing of the pinnæ. No genu valgum or other bony deformities. Height 5 ft. 2 in. Body-weight 6 st. 6½ lb.

Patient has two brothers, the younger of whom, aged 14, is already as tall as he is, and the elder, aged 19, much bigger. The patient is said to have had no serious illnesses, though two years ago he had three epileptiform seizures.

Dr. PARKES WEBER said he thought the renal disease in this case was a form of chronic interstitial nephritis in congenitally defective kidneys, the congenital defect being one of actual dysplasia or of inability to resist infections or toxins. The renal condition was doubtless of the same kind as that present in most cases of renal rickets and renal dwarfism.

Tuberculous Epididymitis in a Boy aged 9, with Pulmonary Infection of Three Younger Sibs.—R. W. B. ELLIS, M.D., and DAVID LEVI, M.S.

John W., a boy aged 9, was brought to the Infants Hospital on October 12, 1937, on account of recurrent winter cough since pneumonia and pertussis at age of 3 years; cough worse recently. Has not lost weight. On routine examination, the left epididymis was found to be hard and considerably enlarged. The mother thought this enlargement had been present for at least a year, but it had never given rise to symptoms.

Family history.—The mother is healthy; a maternal aunt and uncle died of pulmonary tuberculosis before the birth of patient. The father has had a chronic cough, with periods of dyspnœa, for the past two years; recently it has become worse and is now productive. He was found to have extensive disease of the upper two-thirds of the right lung. (Sputum examination: Tubercle bacilli present.) There are three younger children, all of whom have been well until the last four or five weeks, during which time they have had chronic cough. They have not lost weight. In each instance the Mantoux test is strongly positive, 1 : 1,000. Direct examination of stomach washings showed no tubercle bacilli (guinea-pigs injected).

Daphne, aged 5. Weight 34 lb. Skiagram shows considerable enlargement of upper mediastinal shadow, extending into left lung field, and enlargement of right hilum (fig. 1).

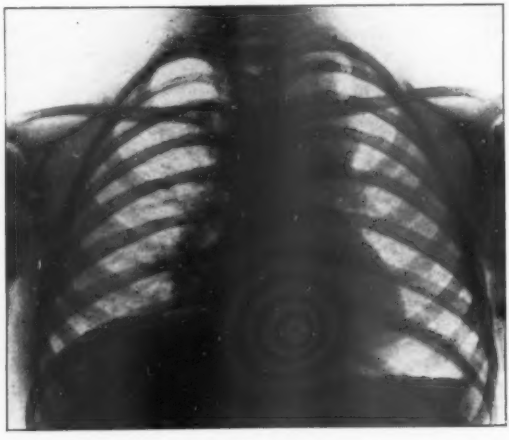


FIG. 1.—Daphne W.

Norma, aged 3 years 5 months. Weight 32 lb. Skiagram shows extensive infiltration around right hilum (fig. 2).

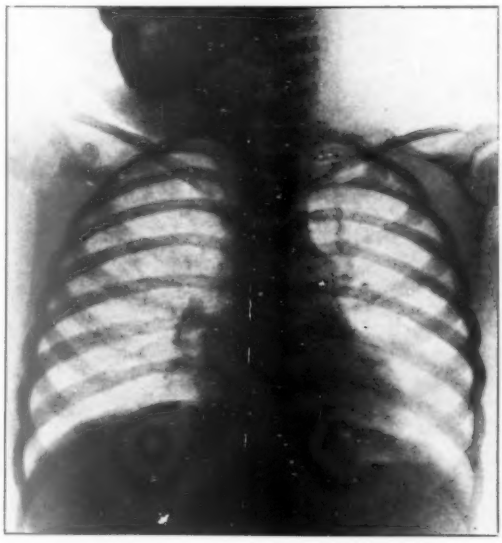


FIG. 2.—Norma W.

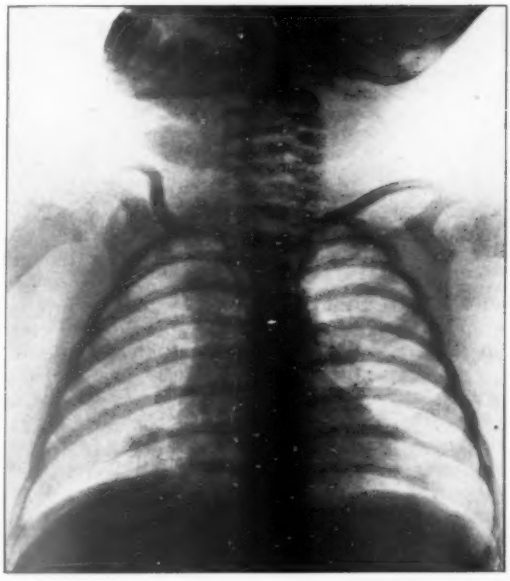


FIG. 3.—Douglas W.

Douglas, aged 1 year 5 months. Weight 35 lb. Skiagram shows enlargement of upper mediastinal shadow to right, and some enlargement of both hilar shadows (fig. 3).

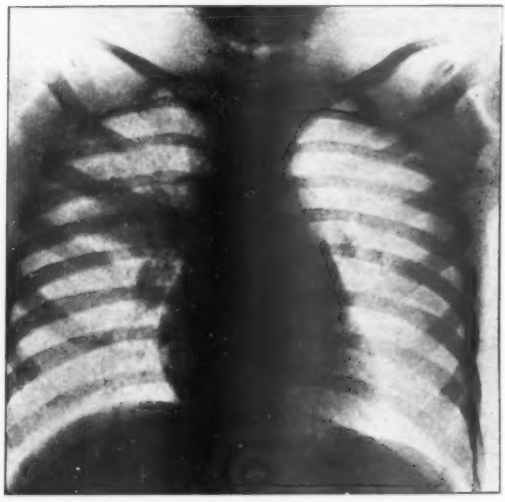


FIG. 4.—John W. Right hilar lesion.

On examination.—John W. is a slender, moderately well-nourished boy. Good colour. No clubbing. Afebrile. The chest moves evenly and there is no impairment of percussion note or diminished air entry. Fine râles are heard posteriorly along the inner border of the right scapula. The left epididymis is enlarged and hard, but not tender. The cord is not appreciably thickened. No enlargement of prostate or vas was detected on rectal examination.

Urine: No abnormalities found. No tubercle bacilli.

Mantoux test: Strongly positive, 1 : 1,000.

Stomach washings: No tubercle bacilli seen on direct examination. Guinea-pig injected.

Radiological examination: There is a flame-shaped shadow extending laterally from the right hilum (fig. 4).

Total Pneumonectomy for Single Pulmonary Cyst.—J. E. H. ROBERTS, F.R.C.S.

J. L., aged 2 years and 4 months on admission to St. Bartholomew's Hospital 27.3.37.

History.—Admitted to Central Middlesex County Hospital in December 1936, with a history of cough and loss of weight, diminished movement, and impaired percussion note on the lower part of the right side. Aspiration of the right side produced air and a little green pus, growing *Staphylococcus aureus* on culture. An X-ray diagnosis of right pyopneumothorax was made on 1.1.37. Rib resection with drainage was carried out. The wound healed without event in five weeks. The child remained dyspnœic, and an X-ray examination showed a large cavity, with displacement of the mediastinum, of considerable extent, to the left side. On 4.3.37 a needle was inserted into the right pleural cavity and a pressure of +10 pneumothorax was recorded. After the removal of 600 c.c. of air the pressure fell to zero, but within five minutes the pressure was again +8. A valvular pneumothorax was therefore diagnosed. The percussion note was hyper-resonant over the whole of the right side and no breath sounds were audible.

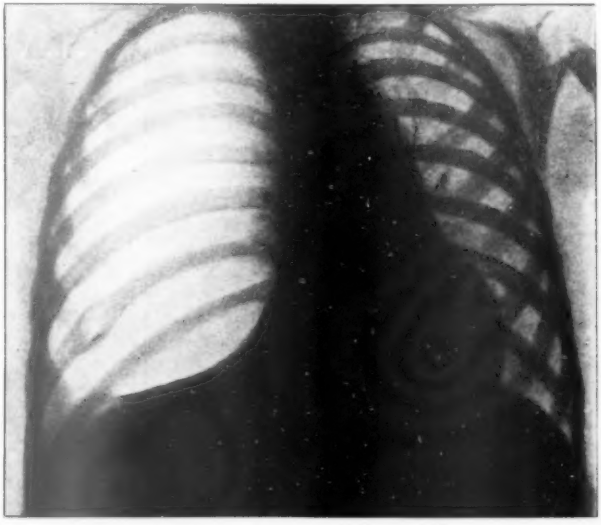
Mantoux reaction (1 : 1,000 K.O.T.) negative.

Blood-count (3.3.37): R.B.C. 5,440,000; Hb. 86%; C.I. 0·8; W.B.C. 5,600.

5.4.37: A thoracoscope introduced through a trocar and cannula showed a cavity lined by a smooth glistening membrane.

7.5.37: Exploratory thoracotomy was carried out under endotracheal nitrous oxide and oxygen by Mr. Rait Smith. A large solitary cyst was found, with much altered remains of lung tissue above and below it. After an attempt to dissect out the cyst, a right total pneumonectomy was performed. A transfusion of 250 c.c. blood was given on the evening after operation, and one of 150 c.c. a week later. A small bronchopleural fistula developed on May 12 and closed during the early part of September.

Present condition.—The sinus is healed. Weight 27½ lb. (Weight on admission 21 lb. 8 oz.) The child is free from sputum, has no scoliosis, and is able to run without dyspnœa. The movements of the ribs on the operated side are approximately the same as on the other side, active McMahon breathing exercises having been carried on throughout.



Cyst of right lung with positive pressure, pushing mediastinum over to left.

Histological report, 10.5.37 (Dr. H. A. Magnus): "The specimen consists of a large cyst lined by a thin white membrane; in one place a vessel can be seen transversing its lumen. About the centre of the cyst there is a small shallow ulcer. The cyst is surrounded by compressed lung tissue which, in places, is somewhat firm and fibrotic, but the bronchi are not dilated and there are no areas of necrosis. Several sections from the cyst wall show it to be composed of somewhat vascular fibrous tissue over which no epithelial lining or remains can be recognized. Sections of the surrounding lung show it to be collapsed and in some areas there is a diffuse thickening of the alveolar walls by fibrous tissue. There is no evidence of infection."

Comment.—This cyst differs from the other solitary cysts of the lung upon which I have operated, in that it is not lined with stratified epithelium. There was no doubt at the operation that the cyst was intrapulmonary, as the pleura was intact over it

and the cyst did not correspond with any of the fissures. It arose, I believe, in the middle lobe.

This child is the youngest, as far as I know, in whose case a total pneumonectomy has been performed.

Total Pneumonectomy for Bronchiectasis: Further Report on Case Previously Shown.—J. E. H. ROBERTS, F.R.C.S.

John L., aged 7.

This child was shown at the meeting held on 8.11.35 [1] having had a total left pneumonectomy performed for bronchiectasis. He is shown now in order that his present condition may be seen, and the improvement in his general mental and physical condition demonstrated.

To show absence of scoliosis 2 years 9 months after total left pneumonectomy.

This child and the one shown by Mr. Tudor Edwards on the same day were both operated on within two days of each other, and were the first two cases to have a total pneumonectomy performed in one stage. It will be observed (*see* fig.) that in spite of the removal of the whole of one lung two years and nine months ago, the child has almost no scoliosis. This is attributable to the continuance of

[1] *Proceedings*, 1936, **29** 219 (Clin. Sect., 9).

McMahon breathing exercises which were instituted shortly after the operation and have been carried on ever since at the Heritage Craft Schools, Chailey.

After having healed, the drainage sinus broke down, owing to the formation of a ring-regeneration in the small piece of rib resected for drainage. A resection of this bony ring was performed, and final healing took place. During the fourteen days' interruption of the breathing exercises necessitated by this procedure, scoliosis rapidly appeared, but disappeared again on the resumption of breathing exercises.

Bronchiectasis, with Repeated Hæmoptysis treated by Postural Drainage followed by Pneumonectomy.—ANDREW MORLAND, M.D.

J. M., a boy aged 15 (Basque refugee). History of cough, sputum and hæmoptysis since age of 5.

Four attacks of hæmoptysis—6 to 20 oz.—shortly after he reached England in June 1937. Admitted to French Hospital July 6. Temperature 105°, 20 oz. foul sputum; almost moribund. Left side of chest dull and contracted; cavernous breathing and bubbling râles. Marked clubbing. Great improvement with postural

FIG. 1.—Bronchogram (lateral) showing saccular bronchiectasis.

drainage, transferred to the Thoracic Unit, St. Mary Abbots Hospital, August 13. Sputum 3 to 8 oz. Temperature normal. Bronchograms (figs. 1 and 2) showed large saccular, bronchiectatic cavities in left lung; right lung normal. In spite of the fact that the extreme fibrous contraction of the left lung was certain to make pneumonectomy difficult, if not impossible, this operation was considered justifiable.

on account of the frequent and severe attacks of hæmoptysis, and was performed by Mr. Tudor Edwards on September 9. The pleura was very thick and adherent both to the chest wall and to the pericardium. Part of the pneumonectomy had, therefore, to be carried out extrapleurally.

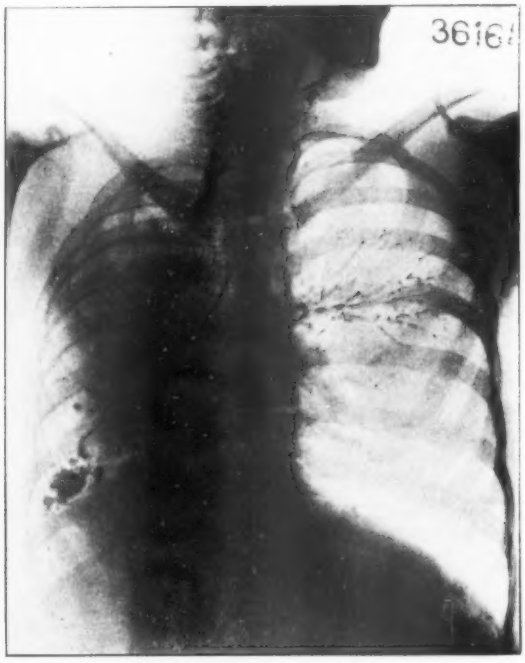


FIG. 2.—Antero-posterior view.

November 12, 1937: Patient has been up for six weeks. General condition remarkably better, trace of sputum, but pleural fistula still present and discharging a small amount of thick pus.

Dr. RICHARD ELLIS said this case had impressed him as much as any result of surgery that he had seen. He had examined the boy before he left Bilbao, and had been doubtful if it would be worth while his embarking, and he had seen him again shortly after his largest hæmoptysis, when he appeared almost moribund. Two days ago the boy had written saying he was "un nuevo hombre", since he had never before known what it was to be free from cough and sputum and the fear of hæmorrhage. The prognosis now appeared wholly favourable, since the lipiodol skiagrams indicated that the bronchiectasis had been confined to the lung that had been removed.

Section of Ophthalmology

President—W. H. McMullen, O.B.E., F.R.C.S.

[*October* 8, 1937]

Defective Movements of Left Eye.—J. Biggam (Major, R.A.M.C.).

C. H., aged 17½. On the evening of September 14, 1936, he began to feel ill, and vomited three or four times. He struck his left orbit on edge of a bucket while vomiting into it during the night. The bruises from this blow were so slight as to be hardly noticeable next day and the eye itself was apparently not affected. When he awoke next morning he had diplopia. He recovered from the "illness" in two or three days but the diplopia continued, though it diminished a little during the first month. He denies eye trouble previous to the accident.

The condition appears to have remained unaltered during the last year.

On examination (3.5.37).—Vision $\frac{6}{5}$ and J 1 each eye. Pupil reflexes, refraction, fundi normal. Convergence good. No ptosis or proptosis. Muscle balance normal, vertically and horizontally, throughout the horizontal plane. Right eye: Movements of right eye full in all directions. Left eye: Horizontal movements full: vertical movements restricted to 10° above and 25° below horizontal. Restriction appears to be that of movements, not of individual muscles. Has binocular stereoscopic vision in the area of binocular vision; diplopia outside this area.

Wassermann reaction negative. Cerebrospinal fluid normal. Complete neurological examination otherwise negative. Radiograms show no abnormality.

Among the possible diagnoses considered were: (1) Congenital defect; (2) direct effects of trauma of accident; (3) a central supranuclear lesion connected with the "illness" and vomiting—such as a localized encephalitis or small hæmorrhage. The last of these appears to be the most likely diagnosis.

[*November* 12, 1937]

Defective Movements of the Left Eye.—R. Affleck Greeves, F.R.C.S.

J. B., aged 7.

Attended out-patient department, February 6, 1937. Four days previously he had struck his left eye on a door-handle; since then he had seen double, one image being above the other. He vomited after the accident and had a severe headache, but was not unconscious.

Right eye: Vision = $\frac{6}{6}$; normal eye. Left eye: Vision = $\frac{6}{9}$. Absence of upward movement and marked limitation of downward movement, but lateral movements present, associated with jerky motion, not a true nystagmus. Pupil reacts normally to light but poorly to convergence.

Examined by Dr. Purdon Martin, who thought the condition probably due to a small hæmorrhage at the apex of the orbit. X-rays revealed no fracture.

On further examination in May a marked improvement was noted, downward movement being practically normal, but upward movement was still defective.

This case resembles that shown by Major Biggam at the last meeting.

Discussion.—The President said he understood that Major Biggam's case was supposed to be one of supranuclear lesion. In the present case the neurologist's view was that it was due to an orbital lesion.

Mr. Harold Ridley said the fact that only one eye was involved was somewhat against the view of a supranuclear lesion being responsible.

Melanotic Sarcoma of Limbus (Epibulbar Sarcoma)—Treated by Excision followed by Radium Therapy.—T. KEITH LYLE, M.Chir.

R. P., aged 60. Seen at the Metropolitan Hospital, April 19, 1937.

History.—Fifty years ago a splash of hot fat left a "scar" on the white of the right eye. This gradually spread over the front of the eye in the form of a "film", interfering with the sight; it has become larger during the last two years.

On examination.—Right eye: Large raised, darkly-pigmented plaque extending over the outer half of the cornea, apparently originating from the limbus at about 9 o'clock. Numerous distended blood-vessels running into the growth in the lower part (*see* drawing).

Pupil active; tension normal; fundus and media normal.

V.A. $\frac{6}{18}$ $\bar{c}$ − 0·50 ⌐ = $\frac{6}{12}$; J 1 $\bar{c}$ + 2·50 added.

+ 1·00 60°

Left eye: Normal in every respect. V.A. $\frac{6}{9}$ $\bar{c}$ + 1·00 = $\frac{6}{6}$; J 1 $\bar{c}$ + 2·50 added.

Treatment.—5.5.37: Excision of growth which stripped off the cornea quite easily but was more adherent in the limbal region. The conjunctiva over the growth in this region was also excised.

2.6.37 and 14.9.37: Surface application of radium at the Radium Institute (Dr. Roy Ward). The dosage of radium on each occasion was an unscreened plaque of 6·2 mgm., having an active area of 1·25 cm. diameter, used in contact with the cornea for one hour. It is proposed to give one further application.

Microscopical section of growth shows a melanotic sarcoma of the limbus arising from nævus cells.

? Neoplasm of the Left Optic Nerve.—T. KEITH LYLE, M.Chir.

M. W., female, aged 50.

History.—First attended the Royal Westminster Ophthalmic Hospital, 17.7.37 complaining that nine weeks previously she had begun to see double. This diplopia lasted for thirty-six hours; it was of a "horizontal" nature, the two images being side by side. The left eye then became very painful, the pain radiating over the left side of the head, down the left side of the nose, and into the upper lip. The sight of the left eye gradually deteriorated. The eye is now completely blind.

Past history.—1922: Right salpingo-oophorectomy for ovarian cyst; 1927: Pelvic peritonitis; 1930: Colpo-perineorrhaphy and subtotal hysterectomy. (N.B.—No evidence of neoplasm of uterus.) The three operations were performed at University College Hospital.

One daughter; alive and well. No miscarriages.

Ocular examination.—Right eye: Pupil reacts briskly to direct light, but is inactive consensually.

V.A.: $\frac{6}{12}$ $\bar{c}$ + 0·75 ⌐ $_{10°}$ = $\frac{6}{6}$. Optic fundus normal. Visual field normal.

Left eye: Pupil is inactive to direct light, but reacts briskly consensually.

V.A.: No P. of L. Pallor of left optic disc. Eye painful on pressure and on movements, which are slightly restricted laterally. Slight left ptosis and proptosis. Sensation to pin-prick and cotton-wool is slightly diminished over the territory of the first and second division of the left 5th nerve.

Investigations.—X-ray examination of skull and orbits: Nothing abnormal discovered. No difference in size of optic foramina.

Ear, nose, and throat examination (Mr. E. D. D. Davis): "Nose, nasal sinuses, throat, and ears normal."

Cerebrospinal fluid: Cells 1 per c.mm. Protein = 0·04%; globulin not in excess; chlorides 0·72%; sugar 0·052%; Wassermann reaction negative.

Blood-count: R.B.C. 4,700,000; Hb. 90%; C.I. 0·9; W.B.C. 7,000. (Polys. 62%; lymphos. 31%; monos. 6%; eosinos. 1%).

I shall be glad to have suggestions as to treatment. Should there be an exploratory operation, or is it better for the present to keep the patient under observation ?

Mr. L. H. SAVIN said that the late Dr. James Collier had described a similar condition to this under the title of "inflammatory periostitis in the sphenoidal fissure", and had reported, some years ago, a series of forty cases[1]. The present case, he suggested, might be of that kind.

At any rate the possibility should be borne in mind before undertaking an exploratory operation.

Detachment of Internal Limiting (Hyaloid) Membrane of Retina.—F. G. FENTON, F.R.C.S. (introduced by Mr. E. WOLFF).

L. A., female, aged 23.

History.—February 1937 : Patient had an attack of acute juxta-papillary choroido-retinitis for which no extra-ocular cause could be found after thorough examination. The condition has now reached a quiescent stage.

On examination.—Atrophic area of retina above and on temporal side of optic disc with corresponding wedge-shaped defect in lower nasal visual field.

Internal limiting membrane of retina (hyaloid membrane) has become detached and lies in vitreous close to posterior surface of lens, appearing as a thin transparent membrane with a round perforation representing deficiency of this membrane at optic disc.

R.V. $\frac{6}{6}$; L.V. $\frac{6}{9}$ $\bar{c}$ + 2·0 sphere.

Discussion.—Dr. A. J. BALLANTYNE said he did not understand how the internal limiting membrane could come so far forward as it appeared to have done in this case, in a comparatively healthy vitreous. On focusing the ophthalmoscope on to the summit of that membrane there was no surface reflex from it. If one focused through it to the retinal details behind, there was the usual retinal surface reflex which was supposed to come from the anterior limiting membrane. It was difficult to see how a reflex of that kind could be obtained if the anterior limiting membrane was out of position to the extent of four or five diopters.

Mr. EUGENE WOLFF said he thought this was what was usually described as a "detachment of the hyaloid". In connexion with a paper which he had read at the last meeting of the Ophthalmological Society, he had shown sections demonstrating that the foot-pieces of the fibres of Müller did not form the internal limiting membrane of the retina but that what used to be called the hyaloid membrane limited both the vitreous and the retina. There was, in fact, only one membrane, whatever name one wished to give it. This membrane often became detached, either as an artefact in the preparation of microscopic sections, or in pathological conditions. It might be in any position from the disc to the back of the lens, in which site he himself had seen it. Pathologically, therefore, he saw no difficulty in understanding that it could come forward.

Mr. RANSOM PICKARD said that his difficulty in accepting it as the internal limiting membrane was that, allowing for the hole corresponding to the disc, the membrane did not appear to be as uniform as one would expect it to be. He thought that if the acute condition was a perioptic choroidal inflammation there would have been vitreous opacities, as there usually were, and some might have condensed into a membrane.

Superficial Epithelial Dystrophy of the Cornea.—F. G. FENTON, F.R.C.S.

D. H., female, aged 57.

The patient came to hospital complaining of irritation and burning sensation in the eye, of some weeks' duration. Before that she had had for two or three months, mild discomfort in the eye. I found the whole cornea, especially the lower two-thirds, covered with discrete superficial spots of staining, some of them confluent.

[1] "Textbook of the Practice of Medicine". Edited by F. W. Price. 1st. Ed., p. 1284.

There was some haze in the superficial layers and all the nerve-fibres stood out markedly as white streaks. There was some diminution of corneal sensation. The condition was treated with simple lotions and, at the suggestion of a senior colleague, I sent her to Charing Cross Hospital, where she had five radiological treatments, which caused a superficial flaking of the corneal epithelium. At the end of the third treatment she said she was feeling decidedly better and more comfortable. At present the condition of the corneal epithelium, seen under the slit-lamp, remains the same as it was at first, but the corneal sensation has improved, and the patient says she feels ready to return to work. I do not know whether the improvement is the result of the radiological treatment, or whether it would have occurred without radiation. I shall be glad to hear opinions on the case.

Discussion.—Mr. BASIL GRAVES said that in 1927 Mr. Gray Clegg and Dr. Mulock Houwer had described a form of conjunctivitis with filamentary keratitis in elderly women suffering from rheumatism or gout or arthritis deformans. Had he not heard any other opinion on to-night's case he would have thought this also might belong to the same class, unless the patient was having something instilled, or some treatment, which could account for the mobile flocculent material on the corneal epithelium.

Mr. FENTON (in reply) said that the flocculent material had appeared since the radiological treatment was commenced. The patient also suffered from rheumatoid arthritis.

***Filaria bancrofti* in the Interior of the Eye.**—W. H. MCMULLEN, O.B.E., F.R.C.S. (President).

N. B. M., male, aged 25, an Indian student, was first seen 8.9.37, suffering from inflammation in the left eye, of six days' duration.

He was referred to me by Dr. Hernaman Johnson, who was treating him with X-rays for spondylitis, from which he had been suffering intermittently since he was 10 years old. No definite cause for this trouble had been found.

About a year previously he had had inflammation of the left eye, which was diagnosed as iritis, and lasted about fourteen days.

I found signs of acute iritis in the left eye, with no special features. The eye was much injected, the aqueous was slightly cloudy with many floating particles. The pupil dilated well with atropine; there were some spots of pigment on the lens. Left vision, with $-$ 0·5 sph. $-$ 1·5 cyl. 180°, $= \frac{6}{18}$. Two days later the eye was rather more injected, some k.p. had appeared, and the eye was very painful.

On September 16 the condition was somewhat worse, the pupil was smaller, folds had appeared in Descemet's membrane, and there was much fine k.p. Left vision, with correction, $= \frac{6}{24}$. Patient was then admitted to a private room at the Royal Westminster Ophthalmic Hospital where he remained for thirteen days. The usual treatment, including application of leeches, proved at first ineffective, pain was intense, and atropine failed to keep the pupil dilated, but one subconjunctival injection of mydricaine produced full dilatation, which was maintained by atropine and cocaine. Steady improvement set in after a week's treatment in hospital.

On October 6 the eye was almost free from injection. Vision with correction was $\frac{6}{9}$. The remaining k.p. was brownish and very fine, and there were only a few particles floating in the aqueous. During examination with the slit-lamp there suddenly came into sight in the aqueous a minute worm-like object, actively motile, very thin, and apparently about $\frac{1}{4}$ the length of the vertical extent of the focused beam from the slit-lamp, say 1– 1·5 mm., but its very sinuous form and very active motility made estimation of length very difficult. It was seen only for a few seconds and apparently disappeared behind the iris.

On October 13 the signs of inflammation had almost completely subsided, and left vision, with correction, was $\frac{6}{6}$ pt. On slit-lamp examination a nematode was again seen and at one time I had the impression that two were present, but movement was so active that it was impossible to be sure of this. Fortunately Colonel Wright was in the house at the time and I was able to get him to examine the case. He agreed that the object seen in the anterior chamber was undoubtedly a nematode, a very young one, much smaller than the one he had seen in the eye in India. Major Cruickshank kindly arranged for the patient to be admitted into the Hospital for Tropical Diseases for investigation, and I have to thank him for the following report :—

> Mr. N. B. M. was born in Calcutta. There are no signs of elephantiasis of the limbs and no clinical signs of filaria, such as enlarged glands, hydrocele, lymph-scrotum, &c. There is no abnormality of the urine ; nothing abnormal was discovered on general physical examination and he is not anæmic.
>
> *Microfilaria bancrofti* are present in his night blood in fair numbers. The differential white cell count is as follows : Neutrophiles 56% ; lymphocytes 13% ; large mononuclears 4% ; eosinophiles 27%.
>
> Filaria skin test negative.
>
> He gives a history of fever, which he called malaria, and which seemed, from the symptoms, more likely to have been malarial than filarial.

Unfortunately the worm was not visible in the eye to-night, but I am able to show a specimen of night-blood containing *Microfilariæ bancrofti*.

The occurrence of *F. bancrofti* in the interior of the eye has been recorded only twice previously, although a few other cases have been published of unidentified filariæ inside the human eye. In 1932 Pillai and Nayar saw a filaria emerging from the retina close to the macula. Nineteen days later the worm was found in the anterior chamber. A small keratonic incision was made into the anterior chamber, when the worm disappeared, apparently escaping from the eye with the aqueous, and was never recovered. *Microfilariæ bancrofti* were found in the blood on several occasions (*B. Journ. Oph.*, 1932, **16**, 549).

In 1934 Lt.-Col. R. E. Wright removed an adult *Filaria bancrofti* from the anterior chamber of the eye of a young Hindu. Its identity was established after removal from the eye. No microfilariæ were found in this patient's blood (*B. Journ. Oph.*, 1934, **18**, 646).

I should like to know what it is thought best to do in this case. Should one wait, or should one let out the aqueous and try to find the worm, or wash it out ? I feel inclined to wait.

Discussion.—Mr. HUMPHREY NEAME said that perhaps a more satisfactory way to get it out would be with an aspiration needle on a syringe.

The PRESIDENT (in reply) said that this was what he proposed to do if he could see the worm in the anterior chamber before operating.

Major BIGGAM said that he had once had an amusing encounter with a filaria of the type found in the eye of the horse. He was called, in India, to see a racehorse which had an enormous filaria, many centimetres long in the anterior chamber. It could be seen, naked eye, lashing about in the aqueous. It had been there a considerable time and the cornea was partly opaque, apparently due to a cirrus-cloud-like opacity in Descemet's membrane. He had made a small incision in the limbal region with an ordinary Graefe knife—he had not realized till then how tough a horse's cornea was—turned the knife crossways, and the filaria shot out in a burst of aqueous. The eye gave no further trouble, but the corneal opacity never cleared up.

Dr. A. J. BALLANTYNE said that in one patient whom he saw at hospital, a filaria was seen crawling about under the conjunctiva, and when it was proposed to remove it the patient said : "Don't put cocaine in ; several people did and it disappeared." The conjunctiva and worm were gripped with forceps, the conjunctiva incised and the worm removed.

Mr. FENTON said that he had a similar experience at the Royal Westminster Ophthalmic Hospital. The patient had come from West Africa complaining of irritation in the eye, and a worm ¾ in. long could be see wriggling about just above the limbus under the conjunctiva. Cocaine was inserted, and then only the tail could be seen. The conjunctiva was quickly cut down upon, and after some difficulty the worm was grasped by its tail and removed. The cocaine produced rapid movement. The pathological diagnosis was guinea worm.

Mr. T. HARRISON BUTLER said that he also had had a case of loa-loa in the eye; the appearance had been exactly that now described. The patient was a doctor from West Africa, and he also had said that if cocaine was used it would drive the worm away. He (the speaker) had grasped the conjunctiva with forceps, put a thread through, and tied a thread round the creature's middle. Then he had inserted cocaine and tried to dissect it out, but it had broken in the middle. It was about an inch long.

The PRESIDENT (in reply) said that Colonel Elliott, in his book "Tropical Ophthalmology", referred to the rarity of filaria in the human eye in comparison with its appearance in the eyes of animals, and said that it was of a different species in the latter. He understood that subconjunctival filariæ were usually loa-loa.

Plasmocytoma of the Lacrimal Gland

By S. T. PARKER, F.R.C.S.

As this condition is exceedingly rare, the following case is of unusual interest.

Clinical history.—In August 1935 A. G., a man aged 66, sought advice, because he and his friends had noticed that his left eye appeared to be gradually closing. This had first been observed ten months previously. It was perfectly obvious at a glance that there was ptosis and some undue prominence in the outer half of the supra-ocular sulcus. The marginal portion only of the upper eyelid was capable of slight voluntary movement. Digital examination revealed a firm, somewhat lobulated subcutaneous swelling, which seemed to be extending from the fossa for the lacrimal gland. All ocular movements were free; no diplopia; vision $\frac{6}{6}$ unaided; normal fundi and media.

Diagnosis of tumour of the lacrimal gland seemed most likely, and was confirmed at operation a few days later. The lacrimal gland, enlarged about two and a half times its normal size, was removed without any great difficulty. It was greyish-brown in colour, slightly lobulated, of firm consistency, although not hard, and definitely encapsuled. The capsule was intact, except at one point, where it seemed to be thin and torn. The bony upper wall of the orbit felt normal, and apparently there was no portion of the gland remaining. Recovery was uneventful. A detailed report from the pathologist at the Royal London Ophthalmic Hospital is herewith given.

SPECIMEN 1. *August 1935.*—The specimen arrived fixed in Zenker's fluid. It was embedded in paraffin and stained with hæmatoxylin and eosin.

Microscopic appearances.—It is a very cellular nodule of tissue. There is a definite attempt at encapsulation by fibrous connective tissue, but the line of excision in places transgresses this capsular boundary, leading one to the conclusion that excision has been incomplete. Fibrous tissue trabeculæ, many of them very thick and solid, enter the substance of the nodule from this capsule, and intersecting in the substance divide it up into lobules. Many well-formed blood-vessels accompany these septa, but very few are found in or amongst the actual masses of tumour cells.

The cellular elements of the mass are, in some places, supported in a very fine connective tissue matrix; in places they appear to be nothing more than solid masses of tumour cells. No areas of degeneration or necrosis are seen. There is remarkably little variation amongst the cells, the only notable one being in respect of size.

The cells are indistinguishable from plasma cells. The cells have undergone slight distortion as a result of fixation but are roughly oval or circular in outline. The cell cytoplasm appears amorphous. The nuclei are round in shape and show a well-staining basophil chromatin network. In many of these nuclei, the arrangement of this network is according to the classical description giving a "cartwheel" appearance! One or two nucleoli are to be seen in most of the nuclei. Mitotic figures are very scarce, though special stains were not used to demonstrate these.

The tumour is evidently a plasmocytoma.

For the first six months no sign of any recurrence was detected, and the patient resumed his normal life of a farmer. Gradually the inner half of the supra-ocular sulcus became obliterated by a second swelling, very similar in size and consistency.

Second operation.—On September 14, 1936, that is, after a lapse of slightly more than a year, this swelling was explored through a second curvilinear incision. A mass of fibrous tissue and new growth, slightly less in size than on the first occasion, was removed. The growth was now adherent to the frontal bone, with some erosion of the floor of the frontal sinus. The mass was removed with the help of a rugine, and the surrounding area was cauterized as freely as possible, by diathermy. The patient made a good recovery, but suffered from troublesome diplopia, through unavoidable damage to the superior oblique muscle. The pathological report on this second specimen is as follows :—

SPECIMEN 2. *September 1936.*—The histological appearances are merely confirmatory of the previous findings. There is a greater preponderance of fibrous tissue; this is consistent with the fact that the specimen was obtained at a second operation. There are areas of necrosis and degeneration, and the cells on the whole take hæmatoxylin stain less well than formerly. There has been much hæmorrhage in the substance of the tumour.

The rest of the specimen consists of orbital contents, many of the blood-vessels show considerable thickening of their walls.

First treatment with radium.—As previous observers had noticed good results with radium, this was applied six weeks after the second operation, and no further recurrence was apparent until ten months had elapsed.

Second radium treatment.—In July 1937 a tumour as large as that first observed two years previously was present. Radium was again tried. This time the needles were more deeply inserted into the mass, and now, three months afterwards, there does not appear to be any trace of further recurrence, but previous experience indicates that this interval of time is obviously too short to suggest that the tumour is permanently eradicated, especially in view of the bony involvement. Ocular movements and vision are still unimpaired. No enlarged lymph-nodes have at any time been detected.

Radiological examinations.—In August 1935 the frontal sinuses appeared normal. A year later a skiagram of the left sinus confirmed the operative findings of bony erosion, and in September 1937 there was further radiographic evidence of this. The rest of the skull, long bones, spine, ribs, and sternum appear normal.

Laboratory tests.—Wassermann reaction negative. Urine tests, especially for Bence-Jones albumose, were negative. The blood is also found to be normal on examination.

Comment

Waldeyer is said to have introduced the word "plasma" cell in 1871. The term plasmocytoma or plasmoma has been used in the past to describe any form of tumour, either neoplastic or inflammatory, composed of plasma cells. The distinctive features of the plasma cell as seen under the microscope are as follows :—

A large cell up to three times the size of a lymphocyte, either oval or more frequently polyhedral in shape. The cytoplasm is clear and on careful examination appears to take more of the stain peripherally. The nucleus is a characteristic feature, excentrically placed, with deep basophilic staining of its chromatin content, radiating not only from a

nucleolus like the spokes of a cartwheel, but also condensed beneath the nuclear membrane. The size of the nucleus varies; in some cases being small, in others large, and not always single. Binucleate forms tend to occur in neoplastic cases. The nucleolus is said by some observers to be acidophil in reaction [1], but this is open to doubt, and is certainly not so in this case. A clear crescentic perinuclear zone in the cytoplasm is demonstrated very

FIG. 1.—Showing tumour after recurrence in July, 1937.

definitely by staining with iron hæmatoxylin. This is said by one writer to be a feature of plasma cells of inflammatory origin [2], but is more likely to be a characteristic of plasma cells in general. This zone can be observed under high power oil immersion in many of the cells in this case, and in most other similar microscopic views of other published specimens. Mitotic forms are common in neoplasms and the average size of the cell is claimed to be smaller if the origin is inflammatory [7].

Origin.—The origin of the plasma cell is unknown. A commonly accepted view is that it arises from a lymphocyte, on the evidence of some who claim to have observed this gradual transition in inflammatory conditions. Another theory is that the origin is from fibroblasts arising in the endothelial lining of the blood-vessels. The only account in the literature of plasma cells in association with the lacrimal gland is by Hannes [14]. In a series of sections from forty-eight normal human glands, ranging from the newborn to those of persons 80 years old, a few scattered plasma cells were present in every specimen. In the very young, lymphocytes were not present in so great a number as in later life, but as age increased there did not appear to be a corresponding increase in plasma cells. This, the author argues, is difficult to correlate with the theory that lymphocytes in the connective tissue are the precursors of the plasma cell. He further states that if there was a hæmogenic origin from the lymphocytes in the blood-stream, one would expect to find aggregations of plasma cells at or near the vessel walls, caught in the various stages of this migration, but none of his sections showed any indication of this. Hannes thought the origin was from the " Bindegewebezellen," or connective tissue cells.

Occurrence.—Rare in females. Commoner in males over middle age [5]: (1) In neoplasms; (2) in inflammatory conditions.

Neoplasms: (*a*) The medullary form, which may occur as solitary plasma-celled myelomas, in the femur, humerus, or tibia [15], or more commonly a diffuse tumour of

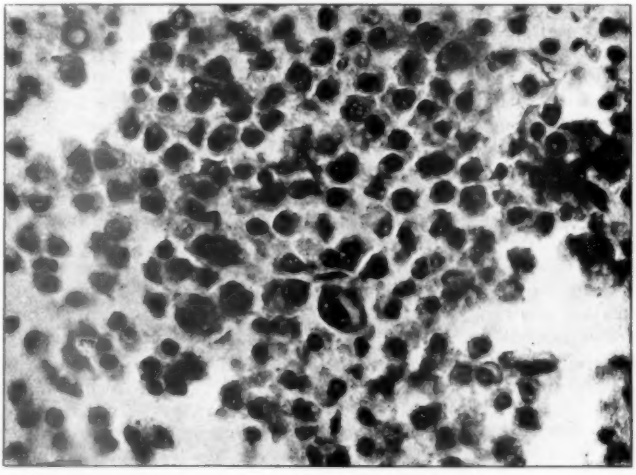


FIG. 2.—Showing typical plasma cells, from lacrimal gland tumour. Pernuclear clear space and characteristic arrangement of chromatin content of nucleus well illustrated. (× 450.)

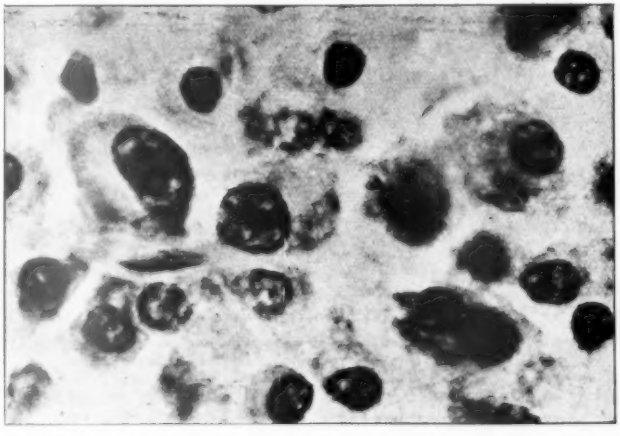


FIG. 3.—Portion of same field as fig. 2, showing typical plasma cells. (× 1500.)

bone-marrow, in long bones (multiple myeloma), in the condition known as myelomatosis. (*b*) Extramedullary type: In the upper respiratory tract, serous membranes, epulides in the mouth, lymph, salivary, and lacrimal glands, and in the conjunctiva.

Bence-Jones albumose is said to be present in about 50% of cases [13] of the medullary type. A similar proteinuria is sometimes present in myeloid leukæmia and carcinoma of bone where there has been diffuse infiltration of the medulla [19].

Inflammatory conditions: Granulomata in the mouth, or similar lesions due to syphilis or tuberculosis.

Blood examination.—The blood examination, in view of recent observations, is of considerable importance. Twelve cases have been described in which there was on the average 20% of plasma cells in the differential white count [19], and another 70% [23]—a plasmocytic leukæmia. In every one the high percentage of these cells was associated with diffuse infiltration in various parts of the bone-marrow of the skeletal system, due to plasmocytoma. Plasma cells occur in the blood-stream in rubeola and rubella, and a few cells, sporadically, in other conditions such as myelomatosis, myeloid leukæmia, metastatic carcinoma, and Hodgkin's disease [9].

Statistics.—In half the cases of myelomatosis the tumours are plasmocytomas [18]. Over 250 have now been recorded of this type, arising primarily in bone. Thirty-four cases of the extramedullary form, including that now reported, have been recorded up to date. In 21 of these the tumours have occurred in the upper respiratory tract. Six in the conjunctiva have been reported by continental observers [12]. As far as one can ascertain no other cases have been recorded of plasmocytoma in the lacrimal gland. In five previous cases there was local recurrence after operation.

The fact that some cases were associated with positive evidence of syphilis or tuberculosis [3], and also that plasma cells have been found in chronic inflammatory conditions [4], has led some observers to consider that these tumours have an inflammatory origin [5]. The uniformity of cellular structure, the gradual increase in size of the tumour, local recurrence and bony erosion by direct spread, is sufficient evidence that this tumour is undoubtedly neoplastic. Local recurrence is not proof that these conditions are malignant, because there is always the likelihood of incomplete removal, but rapid and extensive bone-involvement—a fact previously noted—strongly suggests that these tumours can be locally malignant.

Any neoplasm of the lacrimal gland is comparatively rare. The clear and detailed article on lacrimal gland tumours by Greeves does not mention plasmocytoma. There is the possibility that some neoplasms which he describes under "lymphomas", or "lymphosarcomas" may have been of this nature, and it has been suggested that these conditions have been mistaken for plasma-celled tumours, but the microscopic appearance would at once distinguish the lymphocyte—or even sarcoma cell—from a plasmocyte. A further suggestion has been made that the benign tumours should be called plasmocytomas, and those which recur, plasmosarcomas, but from the histological point of view this is obviously not a helpful distinction.

Microscopic sections of this particular tumour show that in the endothelial lining of the blood-vessels and lymphatic spaces there are numerous cells which Pappenheim's stain proves to be identical with plasma cells. In some of the latter these cells are so numerous as almost to form a continuous lining. This formation cannot be accidental, but supports the theory that the origin of the plasma cell is endothelial.

Conclusions

(1) There is no connexion between the medullary and extramedullary types of plasmocytoma, except the plasma cell.

(2) In this particular case the prognosis is unfavourable. If further surgical treatment is advisable it should be in collaboration with a rhinologist.

(3) Radium is helpful in these cases.

(4) The possibility of plasmocytoma in the differential diagnosis of lacrimal gland tumours should be considered, especially in men over middle age.

(5) Our present knowledge of the histopathology of this condition in so far as the lacrimal gland is affected, does not support the theory that plasmocytomata are of lymphocytic origin, but suggests that they are a type of endotheliomata.

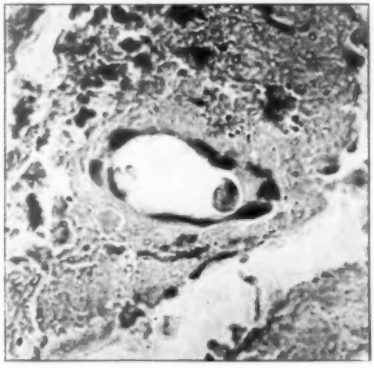


FIG. 4.—Showin cells in endothelial lining of blood vessel, according to Pappenheim's stain, identical with plasma cells. (× 700.)

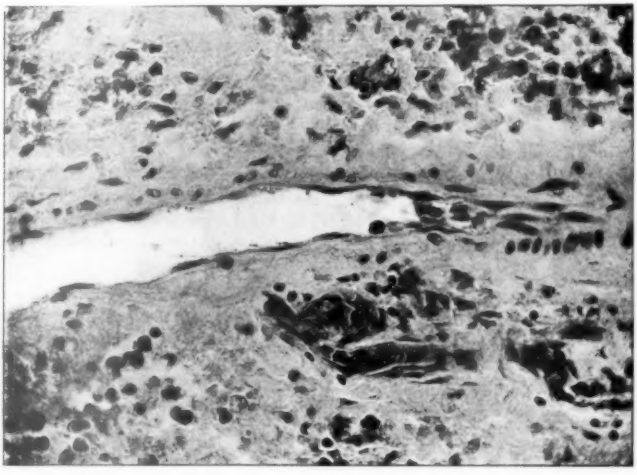


FIG. 5.—Showing endothelium of lymphatic space with numerous cells present identical with plasma cells. Pappenheim's stain. (× 600.)

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Section of Psychiatry

President—E. GOODALL, C.B.E., M.D.

[*November* 9, 1937]

The Neurological and Psychological Effects of Hypoglycæmia

By D. N. PARFITT, M.D., M.R.C.P.

ACCURATE observation of the development of insulin shock is hampered to some extent by the rapid fluctuations in the depth of the insulin effect that is almost uniformly exhibited in the passage from consciousness to coma. Another factor that sometimes complicates the picture is the tendency of the human body to effect its own cure by spontaneous recovery from coma and not only may a patient recover spontaneously while under observation but he may be in the early stages of recovery when the coma is terminated by giving sugar. It is unfortunate, too, that close examination and observation delay the onset of coma and sometimes the signs observed are different from those present when the coma is allowed to proceed with as little interference as possible. Finally, since signs of autonomic activity are prominent and important during the hypoglycæmia one has to remember that the patient may be weighted to one side or another of the autonomic scale before the insulin is given, and that differences are more important than static signs. This particularly applies to cases of schizophrenia.

At Hatton we have followed the usual practice of giving insulin at 7 a.m. or just before, and deep coma has most often occurred a little before 10 o'clock; very often the dose has been varied to produce the shock at 10 a.m. or before, since this is a convenient time and gives space in the morning for the full coma period. The following description of a shock is based roughly on this time relation.

With an injection given at 7 a.m. or just before, there is no constant change until about 7.30, when a mild degree of apprehension, agitation, restlessness, and irritability frequently develops or the patient may appear more alert, talks more freely, and tends to be happy, elated, and boastful. As early as this a slight impairment of reason, judgment, criticism, and concentration can be demonstrated in co-operative patients. Soon after, in schizophrenics, one sometimes sees grimacing and senseless laughter which may increase to hysterical intensity. The patient may complain of various paræsthesiæ such as tingling in the finger tips, stiffness in the hands, or a generalized feeling of discomfort in the skin; giddiness and weakness may be present but they are not prominent complaints with patients lying in bed. Pilomotor contractions appear, especially in the arms; there is slight pallor or, more rarely, flushing; the pulse-rate usually slows five to ten beats per minute but may be much slower than this or faster than normal, the temperature often falls slightly, or falls and rises again, the feet are cold, a slight perspiration appears and—with nausea, hunger and thirst—

suggests parasympathetic overaction, particularly as the pupils are often a shade smaller.

Around about 8 a.m. the patient is typically quiet and is becoming slightly drowsy; he may yawn or mutter to himself. Irritability develops; he resents examination but can be stimulated and persuaded to do his best in response to questions, although slight confusion and memory loss may be noted. Occasionally a fine tremor is seen in the fingers and this may later spread to the arms and become coarser. Perspiration is now apparent on the hands and feet, which are cold; pallor may give place to a general flush, the pulse-rate increases and may be at the 7 a.m. level or a little faster, the respirations are slower and fuller, while the superficial skin reflexes are becoming diminished and the conjunctival reflex may be already absent.

Between 8 and 8.30 the failure of judgment, reason, and attention becomes plain and can easily be demonstrated in those who are co-operative, or in those whose irritability yields to persuasion. Sometimes the patient is more accessible at this stage and an effective response is more easily obtained; he may talk more freely and expose some of his psychological problems, and even patients who are habitually silent may express their feelings in words. There may be senseless hilarity, with foolish conduct and inconsequent replies to questions, but more often the mood is morose and the patient is anxious to be left alone. In the few cases I have observed catatonia when present has increased at this stage.

Various neurological phenomena may appear—slight twitchings around the mouth and sometimes around the eyes and in the hands; articulation rarely shows slight impairment and even more rarely extensor spasms of limbs and body may be observed.

For a period before and after 8.30 there is often, in a ward of 15 patients, a striking silence and stillness—a calm before the storm to follow; each patient is quiet and drowsy, curled up on one side and showing marked resentment to interference. On examination it is found that concentration and attention are very poor, answers show confusion of thought, are slowly given and incomplete, or no response is made at all and one gets the impression, sometimes, of a verbal motor aphasia. If the examination is persisted with, a marked emotional lability is often uncovered; the irritability may flame into anger and aggression, or violent sobs will simulate acute distress, and yet a little persuasion or a slightly humorous remark will bring smiles to the patient's face or lead to bursts of uncontrolled laughter.

Evidence of autonomic activity is variable. Some patients are pale, others flushed; perspiration may be increasing or getting less, pilomotor contractions may be unchanged or becoming well marked on the face, with the patient complaining of cold, and the actual temperature between 95° and 96° F. The skin may be cold and variably moist over the legs, forearms, upper chest, and abdomen.

The first appearances of the heavy sweats which are to follow may be on the dorsa of the first phalanges of the fingers, at the hair line, over the nose, on the feet, abdomen, or chest, and there is no definite order for the various areas.

As a rule the pupils are unchanged or a little smaller, the abdominal reflexes have disappeared, the cremasteric reflex is much diminished, and the tendon reflexes are exaggerated.

It might be advantageous to discuss at this stage the changes that have so far taken place and their significance. One would expect that whatever change is brought about by insulin, the effects would be distributed throughout the whole brain but that the highest centres, speaking generally, would be the first to exhibit recognizable impairment of function, the various changes being comparable to an alcoholic intoxication. To a great extent this is found to be so, and the anxiety, depression, and irritability, or the excitement and elation, illustrate disordered cortical control.

while the increasing confusion, dullness, and drowsiness are expressions of increasing diminution of cortical function. As well as this, the emotional lability suggests affect at the thalamic level and striothalamic signs—tremor, grimacing, and so on—are beginning to show themselves. Compared with alcoholic intoxication, irritability and depression are more marked but this is not surprising, since insulin-shock treatment lacks the happy background that is so frequently the excuse for alcoholic indulgence.

But this is not the whole story. The perspiration, the cold skin, the variations in the pulse-rate, the marked fall of temperature, the pallor, the paræsthesiæ, all suggest a greater influence on the vegetative centres than one would expect with alcohol at this stage, and it is justifiable to assume that, as well as the descending inhibition, there is a coincident direct effect of insulin on the vegetative centres.

A fairly wide variation in individual responses to insulin is to be expected, and more so because the action is a double one. The variety in the incidence and the order of appearance of different signs must be remembered in what follows.

From 8.30 to 9 the drowsiness increases to somnolence and then to stupor; irritability and resistiveness reach a maximum and then diminish as consciousness begins to fade. Usually the patient lies curled up on one side during this transition stage and by 9 o'clock he is often unresponsive to all questions and to ordinary stimulation, although he may still make spontaneous remarks, the speech being slurred. When it is possible to carry out suitable tests, astereognosis, diminution of sensory discrimination, and inco-ordination of muscular movements are frequently found but not to the extent that one might expect. The response by withdrawal and groans to painful stimuli is still well marked.

Some patients remain quiet while the somnolence deepens and eventually pass peacefully into coma, but very often there is a further restless period around 9 o'clock and in some cases this is excessive, with noisy outbursts and violent motor activity.

The twitchings which have been noted as occasionally occurring around the mouth and eyes generally begin to increase and to spread during this period. Small myoclonic movements are seen in the muscles of the hands and then in the arms, lower limbs, and body. The movements are so slight at first that they resemble a fibrillary tremor, and one can look at a big muscle like the gastrocnemius and see small groups of fibres going into myoclonic contraction without any joint movements. These myoclonic movements increase in force and numbers until combinations of contractions produce jerking of whole limbs and finally violent jactitation may throw the patient out of bed. Coincident with this development and spread of muscular twitchings one can frequently demonstrate an increasing motor irritability; thus if at the beginning of this phase the facial nerve is tapped, the muscles of that side of the face respond by excessive and irregular twitches, and this response increases until the same stimulus will produce violent spasmodic contractions of almost every voluntary muscle in the body. In any group of patients these spasmodic contractions will vary from a few twitches in some, to the most violent reactions in others, and the type of reaction though often fairly uniform, can vary a great deal in the same patient in different shocks. Frequently the onset of these movements, as well as many other neurological phenomena, is on one side first, and I have seen twitches commencing on the right side of the face, then involving the right fingers and hand and slowly spreading up the arm to the shoulder before both legs became involved, the process taking twenty-five minutes and being described by one observer as like a slow-motion picture of a Jacksonian attack.

If this type of reaction, representing a lesion of corticospinal pathways, is not well developed, evidences of striothalamic lesions can frequently be observed, but in the fully developed clonic reaction they are often completely masked. Tremor,

choreic movements, athetoid writhing and twisting, with torsion spasms and rigor of muscles, all occur, and grimacing, pouting, and staring eyes may be prominent also.

After 9 o'clock one can usually obtain ankle clonus, but it is not sustained; the tendon reflexes are exaggerated, and the corneal reflexes are sluggish. The first evidence of abnormal plantar responses can often be found now.

Perspiration, which may have been less for some time, now becomes profuse, and salivation becomes obvious. Large beads of sweat collect on the face and body and the saliva dribbles from the mouth. If the early pallor has persisted, it is commonly replaced at this stage by a normal colour or by a deep flush, with the body, shoulders, and thighs warm to touch, the hands, feet, forearms, and legs remaining cold. Rarely the pallor increases to a deathly hue and the patient appears profoundly shocked. Typically the pulse-rate increases 10–30 beats above the normal rate and is variable; the systolic blood-pressure is raised and the diastolic lowered, the pulsation of blood-vessels is very prominent in the neck, and the pupils may show their first real dilatation. This sudden increase in autonomic signs represents the arrival of the descending process of inhibition at the vegetative level causing disordered function. Higher levels are still showing signs of disordered activity. Sucking and champing movements of the jaws and mouth may be seen and the patient may suck his biceps. Automatic and reflex grasping and unconscious purposive movements may also be in evidence, but disappear before coma. If catatonia was present it disappears.

With the approach of coma the myoclonus and jactitation tend to subside, small myoclonic movements being visible in large muscles after the grosser movements have all disappeared. Response to painful stimuli is fading; first the pin-prick fails to elicit any movement, and afterwards response to forcible supra-orbital pressure also disappears.

Restlessness is often present, with spasms of respiratory difficulty, stertor, flush, and a rapid pulse, alternating with comparative repose.

As the myoclonus dies away, there develops a gradual increase of muscle tone, usually on one side first; the lower limbs are thrust out in extension and the arms rigid in flexion, the greatest tonus corresponding to each wave of respiratory distress. The spasms of tonus may last only a few seconds at first, but they gradually lengthen in duration and occur more frequently; in the intervals the arms may straighten or wave about; the lower limbs may be comparatively flaccid, or walking movements may be made. Trismus may catch the tongue; head rotation and eye deviation and strabismus are common.

There is often a tremendous outflow of perspiration and saliva at this time; the skin is rapidly getting colder, and the temperature is too low to be recorded with an ordinary clinical thermometer.

Sometime before 10 o'clock coma is complete, as measured by disappearance of the corneal reflexes. The plantar responses are extensor; ankle and patellar clonus can be obtained, and the tendon reflexes are exaggerated, including the jaw-jerk, which is easily elicited.

A slow horizontal nystagmus or rolling of the eyeballs is frequently seen at this time, the double swing taking from five to ten seconds. Hippus is another interesting phenomenon which is fairly frequent, the pupil varying in size from a small normal to a large normal, the cycle from large to large taking about a half minute. Later the pupils become sluggish in their reaction to light, and irregularity in pupil contour is sometimes observed. These various signs indicate that the descending inhibition is beginning to cause dysfunction of bulbo-pontine centres.

As the coma deepens, the fluctuations that have been described as the result of a struggle for dominance by insulin and adrenaline [14, 16], become more apparent. They may be absent and the coma quiet and easy, but very often—following a phase

in which the pupil is normal in size, the pulse-rate about 90, the breathing quiet and easy, muscular tonus comparatively low, and the blood-pressure a low normal—the tonus quickly increases and the tonic spasm previously described develops, together with a pulse-rate of 150, a big rise in the blood-pressure, both systolic and diastolic, dilated pupils, forced and noisy respirations, with congestion and cyanosis, and a great increase in perspiration. These spasms often increase in intensity, the lower limbs remaining in extension and the arms changing from flexion to extension. Physiological extension of the toes, with foot inversion and pronation of the extended arms, are later added to this picture. The dilatation of the pupils in these attacks is, of course, quite different from the hippus previously described, which was accompanied by no other particular changes. It will be noticed that the so-called adrenaline attacks are not typical of the action of adrenaline—witness the extreme respiratory difficulty and, less important, the increase in perspiration and the flush. While hypoglycæmia almost certainly calls forth adrenaline the changes are best considered purely from the angle of mechanisms originated by brain changes.

The spasms may subside or may increase in severity and duration, or the severity may lessen and only the duration increase. With a prolonged spasm, the patient can be lifted from the bed and stood up, and with slight support aimed at keeping him upright he will maintain the erect posture. This represents almost a clear-cut decerebrate rigidity.

If the physical condition of the patient permits, the coma may be allowed to deepen still further. The excessive tonus diminishes, the exaggerated tendon reflexes give way to small reactions and finally disappear, the plantar responses can only be elicited with a sharp pin and not with a blunt point, and then they disappear too ; the pupils become so sluggish that if the lid is lifted and the pupil exposed to light it will take perhaps twenty seconds to reach its smaller size and finally no reaction to light will be obtained. Clonus, after reaching a maximum, dwindles away, and sweating and salivation are absent. The pulse becomes irregular and pallor may again develop. Usually before this stage is reached shock is terminated by giving sugar through a nasal tube.

Recovery

The flooding of the blood with sugar may so upset the metabolism of the brain that there may be a momentary deepening of the coma, but in general there is a rapid recovery backwards through the stages described. If the coma is deep and tonus has diminished there occurs a tremendous extensor spasm, with profuse perspiration and respiratory distress. This soon diminishes ; the corneal reflexes return, the plantar responses become flexor, response is obtained to painful stimuli, athetoid or choreic movements may be seen, and in about twenty minutes the patient is conscious but resistive and irritable. Later he becomes pleasant but quiet, or shows emotional lability and behaves foolishly, and finally, in thirty minutes or a little more, is in his usual mental state. These changes are extraordinarily more rapid if the sugar is given intravenously.

Migraine [28], aphasia, and hemiplegia [58 and 60] have been described after recovery. Amnesia for the coma period and for an hour or so before is the rule, with a patchy amnesia for some time before that. Occasionally amnesia is retrograde to the previous evening, especially following shocks complicated by fits.

Variations in the Order and Appearance of Signs

It has already been pointed out how often the various neurological signs appear on one side first, and this has been explained by the greater vulnerability of the dominant hemisphere.

As well as this, one sometimes sees strange inconsistencies in isolated cases. Thus I have seen the plantar responses become extensor in a conscious patient before 8 o'clock and remain extensor until late afternoon, long after consciousness had been fully regained. Certain tendon reflexes may disappear extraordinarily early and then return or remain absent; the corneal reflexes may be unobtainable while the patient is still capable of confused answers to questions, and occasionally the light reflex disappears early and suddenly. A full list of such variations would be endless, but one should stress the complete absence of perspiration that sometimes occurs—the dry shock, which is said to increase the liability to dangerous complications, and particularly to epilepsy, which will be dealt with later.

An occasional dangerous complication is laryngeal spasm, which may develop suddenly at the height of extensor spasms. Three of 22 patients who completed the course at Hatton developed this. More than one attack in the same patient has been reported [59] and one of our three had seven attacks, the other two having one each.

The conjunctival reflex may be absent before insulin is given, or it may be present almost until coma develops, but typically it disappears early, the loss, as with other reflexes, following a fluctuating course. The first disappearance is at the corners of the eye, and the responsive area shrinks centrally until it finally disappears at the corneal edge.

The corneal reflex shows an early increase in sensitivity when general irritability is developing, but thereafter there is a progressive diminution, the loss spreading inwards to the centre so that finally it can only be elicited over the pupil. The reaction here becomes sluggish and then can only be produced by a summation of stimuli-first two or three, then three or four, successive touches with a wisp of cotton, wool having to be made before a response appears, and finally it disappears altogether.

Spontaneous extension alternating with flexion may be the first sign of alteration in the plantar reflex which, when tested, may show dorsiflexion of the ankle and all the toes, followed by a series of successive flexions. Usually a crossed extensor response, the reflex being flexor on its own side, develops on one side only, and this is followed by a double crossed extensor with one or both homolateral responses flexor. Later, both plantar reflexes produce homolateral and contralateral extension, and finally the extensor response can only be obtained from the same side.

Mental Symptoms of Hypoglycæmia

The mental symptoms of hypoglycæmia that may occur in presumably normal people should be remembered when an attempt is made to understand the symptoms occurring before and after insulin shock. It has been stated that the type of reaction is dependent on inborn tendencies or weakness [69] and that any psychosis may be simulated, particularly organic psychoses [30]. Manic [27, 30, 63] states, confusions [27, 30], paranoid, catatonic, and hallucinatory conditions [30, 63], hysterical states and other functional nervous disorders [30, 27, 36, 52, 63], automatisms, amnesias, stupor, depression, narcolepsy, and changes in behaviour, have all been described. It will be clear from this that deductions from psychological evidence afforded by schizophrenics during treatment by insulin shocks can only be made with great caution.

Sakel maintains that if a patient is quiet when sugar is given he is quiet for the rest of the day, and that if he is struggling and restless when the coma is interrupted he remains excitable throughout the day. The mood of the psychotic is known to be prolonged, but I have not observed this close association between the state when sugar is given and the waking state, and I have seen patients who came round excited

whenever sugar was given, and others who were quiet and pleasant when conscious, even if sugar was given when they were restless.

One sometimes sees a steady improvement in the manner of awakening, noisiness and excitement giving way to quiet and pleasantness in succeeding shocks.

Apart from schizophrenic symptoms hysterical manifestations have been commonest in the recovery period, in my experience. One male patient developed great powers of imitation and, refusing to be beaten by any other patient, showed hysterical fits, confusions, amnesias, and every type of reaction which he observed in those around him, although I am sure that his attacks were not malingering. Other hysterical manifestations have been in the form of screams and laughter and rage reactions.

Fear and anxiety are often observed, and it has been suggested that patients work off genuine anxiety in this way, or in states of excitement achieve catharsis—in the psycho-analytic sense.

Lucid intervals have been described by Sakel and others as occurring before and after insulin coma, but I have not seen them. Before coma I have noticed an increased willingness to talk, on the part of some patients, an increased friendliness and sociability with others, but these observations can easily be explained by cortical inhibition, by the diminution of fear that comes after many insulin shocks, and by the general mental improvement one sometimes notices during treatment. After coma I have seen a wide variety of psychological symptoms but, with two exceptions, nothing that could not be explained as an insulin symptom, or as a symptom that might be expected in a person recovering from coma, or, finally, as the expression of general mental improvement. The two exceptions concern male patients with chronic schizophrenia, of the dull, solitary type, who were more pleasant, talkative, and helpful immediately after their shocks than at any other time, but this reaction disappeared while they were still under treatment. Occasionally, improving patients express delusions after coma, revealing that they are not yet recovered, and this has been called reactivation of the psychosis, but such an expected event hardly deserves a special name.

Complications

The remarkable hyperexcitability of the nervous system—and especially of the motor nerves to skeletal muscles—which is often observed, the occurrence of carpopedal spasms with typical attitudes, and of laryngospasm, and an occasional positive Trousseau's phenomenon, have raised the question of the relation of such attacks to tetany [48, 56]. In tetany twitching of the muscles around the mouth sometimes precedes epileptic fits, which may develop into status epilepticus, and the tonic spasms may spread to most of the muscles of the body [47], the resemblance being therefore very close.

There is experimental evidence that in alkalosis the calcium content of the blood is reduced [65] and in hypoglycæmia there is said to be alkalosis [16] but no significant changes in blood or cerebrospinal fluid calcium have been reported [15], and our results confirm this. True tetany may occur, however, with a normal blood-calcium [47], the explanation being put forward that only the ionized fraction of calcium is sedative to the nervous system.

Treatment with parathormone and calcium gluconate has proved useless in this type of case [48], and it is highly probable that the mechanism of production of the condition is quite different from that producing ordinary tetany.

Convulsions are a well-known complication of hypoglycæmia ; they may occur before, during, or after coma, and in a course of 50 shocks they tend to be concentrated mainly in the first third. In the opinion of Sakel and Müller they often herald mental improvement, but I have not observed this. The incidence of reported fits has been

in from 30% to 45% of patients and affected patients have averaged about three fits each [30, 49]. At Hatton 17 of 22 patients who received a full course developed fits, the average number being something over five per patient. The fits are said to be more frequent in dry shocks [60], and hydration of an irritable cortex has been suggested as a cause [21, 30, 55], together with increased cerebrospinal-fluid pressure [1, 18, 55]. Day [14] has stated that the pressure falls with the onset of coma, but 80% of our cases had a considerable increase of pressure during coma.

Experiments on decerebrate animals in hypoglycæmia [40, 53, 74] suggest that the convulsions are due to the irritation of centres in the pons or medulla, being akin to those seen in asphyxia.

It has been claimed that the fits of hypoglycæmia bear no relation to ordinary epileptic attacks because epileptics, whether traumatic, idiopathic, or schizophrenic, fail to develop attacks when insulin is given in shock doses [4, 14, 16, 73, 75], but I have to report quite different findings from this. Two schizophrenics, with histories of seizures, developed frequent fits under treatment, the attacks occurring about an hour before coma was expected, and a young epileptic, who had not had a fit for several months and was kept on her usual dose of luminal, had six fits in a few days when undergoing shock treatment, none of these occurring during coma, two being early in the morning and four soon after coma.

On the basis of the evidence available I am inclined to the view that the convulsions of hypoglycæmia are of two kinds, at least—one group comparable to the so-called idiopathic epilepsy and developing while the cortex is experiencing metabolic changes and is still irritable, and the other group appearing during coma when the cortical functions are inhibited—the medullary fits.

I think it possible that one only sees the idiopathic variety when epilepsy is latent or manifest, and if this is so it should be possible to obtain some idea of the relation of schizophrenia to epilepsy. It will be clear that one or other type or both can appear in any patient.

Status epilepticus is a dangerous extension of the epileptic diathesis. In one case which I observed the patient had three fits after coma, five fits on the morning of the next day, and 15 fits at ten-minute intervals on the third day, her condition being desperate for some time although she eventually recovered. There was no personal or family history of epilepsy.

Slow recovery of consciousness after a nasal feed is a common complication and in true cases even intravenous sugar leaves the patient confused, dull, and irritable, and complaining of malaise and headache which may be followed by a slight evening temperature. In more severe cases the transition from coma to rousable stupor is often marked by late tonic spasms and respiratory disturbances and the symptoms may last into the next day.

In the severest cases unusually violent tonic spasms with opisthotonos are accompanied by an extreme degree of respiratory distress, cyanosis, and protruding eyes, with profuse perspiration and a weak, thready pulse, the worst symptoms developing as late as two hours after the first sugar was given. Between the spasms the general condition is improved and the cerebrospinal fluid pressure which is high during the spasms falls to something over normal. If this anxious period can be safely passed a quiet coma punctuated by bursts of restlessness develops, the plantar reflexes are extensor and the corneal reflexes absent, the condition having some resemblance to a state of concussion. In fatal cases hyperpyrexia has supervened but the temperature usually rises to 103° F. or less, and the pulse is rapid but full and regular. Retention of urine occurs and necessitates catheterization; the urine contains albumin, and nearly always sugar as well, from the excess given in treatment. The transition from coma to rousable stupor may take many hours, or several days, and physical recovery then takes place.

The most striking instances of mental improvement that I have seen have followed this complication, which is probably accidental, but if it has any significance it is difficult to see how one could take advantage of such knowledge.

The condition is not due to hypoglycæmia, for the blood-sugar may be repeatedly raised to 1,000 mgm. % by intravenous injections and never fall below 150 mgm. % and yet the coma remains unchanged.

I have tested the effect of excess sugar, given by the tube and intravenously, on other patients, without ill-effect. Cerebral œdema [55] is an unlikely cause, since the condition is not relieved by hypertonic glucose, nor does hypotonic saline have any effect, while alkalosis [73] can be ruled out, because overbreathing, occurring in the shock, or induced by re-breathing or by carbon dioxide—produces no ill-effects.

This complication almost always shows itself early in treatment and may be associated with a too-rapid increase in the dose of insulin, while it is sometimes preceded by slow recovery in a previous shock. I have not noticed any relation to the duration of coma.

The pathology probably concerns local disturbances of carbohydrate metabolism in the brain-cells, the symptoms and signs, and the resemblance of some of these to encephalitis lethargica, suggesting the involvement of extrapyramidal centres in the mid-brain [62].

Pathology

The underlying pathology of insulin coma is very difficult to determine. Insulin itself is non-toxic, for 1,000 units have been given with sugar in twenty-four hours for diabetic coma without ill-effect [48] and the same fact negatives the suggestion that insulin activates or liberates some other toxin. Nor are insulin preparations poisonous, for only occasional urticaria has been reported. The changes, as a general rule, are functional, since they can be reversed so easily. The actual blood-sugar level is not very important, for symptoms have been noted with a blood-sugar of 150 mgm. % [74], and a blood-sugar level of 15–20 mgm. %, maintained for some time, failed to produce coma [14], but the speed of fall in the level of blood-sugar does seem to be important [35]. It has been claimed that if the cerebrospinal fluid sugar is reduced below 30 mgm. per cent., coma follows [16]. The cerebrospinal fluid sugar level is lower than that in the blood, but when the blood-sugar is reduced the fall in the cerebrospinal fluid occurs more slowly and may still be continuing when the blood-sugar level is rising.

The respiratory quotient of the brain is unity and its food is carbohydrate. Insufficient glucose is said to raise the cellular osmotic tension [17, 48], and this could occur in hypoglycæmia, while vitamin B_1 may have some connexion with the changes that take place [22, 55].

There is evidence that during hypoglycæmia the brain uses less oxygen and sugar [1] and on the basis that dextrose is essential for the utilization of oxygen it has been suggested that anoxæmia leads to asphyxia of brain-cells [33, 44, 53, 54]. Post-mortem findings have been compared with those found in eclampsia, uræmia, and ligature of the carotid arteries, and said to support the asphyxia theory [48], and it is claimed that the same pathology occurs with insulin adenomata.

The interrelation of the internal secretions is well recognized, control being effected through the pituitary body or from a centre in the pons [45]. Adrenaline is the most obvious antagonist to insulin, and there is evidence that the secretion of adrenaline is maximal during hypoglycæmia [74], and in the absence of suprarenals or in Addison's disease [12] the effect of insulin is greatly increased. Leucocytosis [15, 23, 32], and increased pulse-rate, pulse-pressure, and basal metabolism [32] which occur in hypoglycæmia, are said to be adrenaline effects and the delayed coma following

examinations [2] and anger [19] are also stated to be due to adrenaline, the importance of this having been repeatedly stressed [1, 8, 26, 41, 71].

I think it probable that insulin calls forth adrenaline in the early stages of hypoglycæmia, acting through the vegetative centres, but that as the inhibitory effect of insulin descends, this mechanism is thrown into disorder and excessive autonomic instability results. Later there is great diminution in autonomic effects as the inhibition of function increases.

Thyroxin and the diabetogenic hormone of the pituitary are also antagonists of insulin, and their secretion may be increased during hypoglycæmia while their own antagonists and insulin supporters—the internal secretions of the parathyroids and ovaries or testes—may then increase in turn, a general glandular stimulation being thus produced.

Sakel has suggested that besides a general tonic effect, insulin has two important actions. Firstly, by abolishing many nervous pathways, it revives strong primitive nervous responses, and in the process of recovery the nervous mechanisms associated with older habits of thought are less affected than those associated with recent ones and have a chance to recanalize. Secondly, insulin has a specific vagotropic action on the vegetative centres. I believe that the effects covered by the first of these actions would be equally well attained with prolonged narcosis, and if prolonged narcosis is a comparative failure in the treatment of schizophrenia—and I believe it is—one is left with the effect of insulin on the vegetative centres and the possible stimulation of internal secretions. This possible light on the pathology of schizophrenia is surely of the greatest importance.

Cases have been reported in which organic changes in the region of the vegetative centres, with or without other organic lesions, have been associated with hypoglycæmia [7, 13, 30], and if the sugar level alters in such lesions, it is usually downwards, except in pituitary lesions, and even here hypoglycæmia may occur [42]. This suggests that the sugar level is controlled by hypothalamic centres and in this connexion the frequency of abnormal sugar curves in schizophrenics should be remembered [14, 38, 39, 43, 68, and others].

The opinion has been expressed that the good results of insulin shock therapy depend only on emotional shock and psychic trauma [6], and certainly the treatment represents a very forcible presentation of reality to those who are losing touch with it, for although there is amnesia for more than the coma, yet much psychic distress can be occasioned in the pre-coma period and one can easily observe fear, active resentment, or grim forbearance, in the insulin ward.

Improvement or cure has to be established as occurring apart from the temporary benefit of this enforced contact with reality, apart too from any tendency of recent cases to improve in hospital, and apart from the effects of concentrated and prolonged attention. If this proof is forthcoming a step will have been taken towards the elucidation of the pathology of schizophrenia.

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JOINT DISCUSSION No. 1

Section of Medicine with Section of Therapeutics and Pharmacology

Chairman—H. LETHEBY TIDY, M.D. (President of the Section of Medicine)

[*October* 26, 1937]

DISCUSSION ON THE TREATMENT OF BACTERIAL DISEASES WITH SUBSTANCES RELATED TO SULPHANILAMIDE

Dr. Leonard Colebrook (*Abbreviated*): I propose to speak only about streptococcal infections and their treatment with substances related to sulphanilamide.

The first step towards the introduction of these substances dates back to the time when the German chemists satisfied themselves that aniline dyes for certain fabrics had to be built somewhat on the lines of prontosil, with a double nitrogen linkage between two benzene rings and a sulphonamide group in the para position on one of the rings. Next, someone, whose name is unknown, made the intelligent guess that this same constitution might confer a destructive affinity for certain microbic protoplasms. Then, in their methodical way, the German investigators infected animals with all the pathogenic microbes they had on hand and treated them with aniline dyes of this type. It was found that the substance sulphamido chrysoidine, now known as "red prontosil", would protect mice against hæmolytic streptococci, not only when given by the same route by which the mice were infected, but also when given by a different route, and after some hours. Then the French workers, Tréfouël, Nitti, and Bovet, showed that the double nitrogen linkage was not essential for this curative effect. Para-amino-benzene-sulphonamide, which had been known to the chemists for thirty years, was just as effective. Numerous modifications of this substance have been made, but as long as the sulphonamide group has been left intact in the para position, most of the compounds have been effective in curing infected mice.

At this stage I should like to call your attention to the serious problem that is facing us as the result of the introduction of so many trade names for these substances. Something ought to be done about it, though I do not know what. For example,

there are already sixteen trade names for para-amino-benzene-sulphonamide. Sulphanilamide was suggested by my colleague, Dr. Fuller, as a suitable abbreviation for para-amino-benzene-sulphonamide, and it has met with acceptance as a suitable name for this class of substance. The name " prontosil album " has also been given to sulphanilamide and has caused, and will cause, considerable confusion. By registering the name " prontosil album ", the Germans, despite the debt of gratitude we owe to them for their original prontosil, have done a great dis-service to the progress of medicine, since so frequently now the term " prontosil " is used without any qualification, making ' confusion worse confounded '.

To return to the action of sulphanilamide. It was shown that this drug had remarkable antibacterial properties not possessed by red prontosil. These properties are different from those of the ordinary antiseptics which kill microbes well in water, less well in serum, and hardly at all in blood. With sulphanilamide the reverse is the case. It kills streptococci very well in blood, nearly as well in serum, but very little in water. The blood of patients treated with sulphanilamide also shows a greatly increased power of disposing of the streptococci. This latter effect has been challenged by some of the German workers. If you mix blood, streptococci and sulphanilamide, in a stoppered tube with limited aeration, you get the effect I have described. The control blood kills very few streptococci, while the sulphanilamide blood kills enormous numbers. If the experiment is carried out under conditions permitting of free aeration you get a rather different result. This may explain the divergence between our results and those of the German workers. It is conceivable that these drugs act as " internal antiseptics " in the body and that there is a direct killing of streptococci in both blood and tissues, but we cannot be sure of that.

Red prontosil does not possess these antibacterial effects *in vitro*. Nevertheless, one can demonstrate an increased killing power towards streptococci in the blood of patients treated with red prontosil (i.e. the soluble form). This phenomenon, however, appears later, after the lapse of many hours. The explanation of this has been given by my colleague, Dr. Fuller, who has shown that the red prontosils are, in large part, converted by the body into sulphanilamide and excreted as such. This is, in my opinion, the most important fact we have with regard to these drugs.

A further important fact, to the elucidation of which Dr. Fuller has again largely contributed, is the extreme diffusibility of red prontosil and sulphanilamide, as a result of which they rapidly reach the blood, urine, cerebrospinal fluid, and milk. This is probably an important factor in their therapeutic action. Furthermore, these substances are of a low order of toxicity in man and animals.

During the last few months substances have been described by Buttle and his co-workers (1937) which are of special interest because, although they differ considerably from sulphanilamide and are almost certainly not converted into that substance in the body, they have a very high curative activity in streptococcus-infected mice.

Now I shall deal with the evidence of the effectiveness of these substances in man. Our Chairman, Dr. Tidy, has described this as a fact, and I think all the world is accepting it as a fact, but it is right that we should preserve a critical attitude.

I will show you the results we have obtained at Queen Charlotte's Hospital and discuss them briefly. They refer to puerperal fever, but this is not to be regarded as an infection distinct from medical and surgical sepsis. It is nothing more than the infection of a wound by the same strains of hæmolytic streptococci as those causing surgical sepsis, cellulitis, tonsillitis, scarlet fever, and many other conditions.

We have taken the figures for the five years before the introduction of prontosil as a standard of reference. During these five years we did not consider that there was any specific treatment worthy of the name. The death-rate for this period did not vary very much, averaging 22·8%. During the whole of 1935 the death-rate was as high as ever; from the beginning of 1936, when we began to use red prontosil, up to the

present, our death-rate has been 5·5%. Sixty-five cases have been treated with the two red prontosils in combination, and 115 cases with streptocide, a preparation of sulphanilamide. Twenty-one cases did not require treatment. Along with the falling death-rate, the course of the fever has changed considerably. During these last two years the temperatures have usually come down in two or three days after treatment with these drugs, and stayed down, instead of gradually coming down and oscillating for a week or two. Parametritis, which formerly was the bugbear of our puerperal fever wards, has now almost completely disappeared, except for cases due to infections other than hæmolytic streptococci.

Are we justified then in considering that these results—which cannot be doubted—are due to the drug ? Or may there be any other explanation ? Mr. G. F. Gibberd, in a thoughtful paper given at the British Medical Association at Belfast, discussed whether there might have been a diminished " invasiveness " of the streptococcus during this period of improvement.

Such a change would have the same kind of effect on the figures as we have seen, and during the last fifty years a similar change has occurred in the course of scarlet fever. If, however, it has also happened in puerperal fever it has happened rather suddenly and coincides with the introduction of prontosil. There have been slightly fewer cases with positive blood culture, fewer cases with signs of general peritonitis, but if we have a drug which is effective this is to be expected. It becomes difficult, therefore, to be sure about diminished " invasiveness ".

To obtain further evidence on the point, my colleague, Dr. Fry, has selected for study all the cases showing positive evidence of " invasiveness " during the past seven years, i.e. cases in which hæmolytic streptococci were demonstrated in the blood-stream. From 1932 to 1935 such cases showed a 71% mortality, while for the 22 cases in the last two years there is a case mortality of only 27·3%. It is very suggestive that, in spite of these cases belonging to the invasive class, the drug has had an effect.

Furthermore, Mr. Gibberd thought it right to take into account only our puerperal fever results, from which it is difficult to draw an absolutely definite conclusion. But if you take all the evidence, as we should, it seems to me to establish an extremely high degree of probability. By " all the evidence " I mean evidence that animals are certainly cured ; the fact of the greatly increased bactericidal power of the blood ; and thirdly, the fact that cases are now recovering which formerly did not recover, or at least under circumstances which make it almost impossible to believe that the drug was not responsible for the recovery.

One such case has been described by Purdie and Fry (1937). It was that of a woman who had a continuous suppuration, due to hæmolytic streptococcus infection, for a period of three years. The streptococci disappeared entirely within three weeks from the commencement of treatment, and in six weeks the patient was completely healed for the first time in three years. Other cases of this type, which are valuable as evidence, are cases of meningitis. Gray, in America, from a careful study published in 1935, concluded that the recovery from hæmolytic streptococcus meningitis was less than 3%. He found only 66 such cases in the literature for the whole of this century. In the last few months there have been nine cases described in English and American literature alone,[1] and this is strong confirmatory evidence that these substances do act on the human subject.

In medicine we habitually have to act on probability rather than on complete certainty ; the evidence in regard to these new compounds seems to me amply sufficient for such a basis of probability. We may well keep our minds open, however, to the possibility that we have attributed too much to the drugs and too little to spontaneous recovery.

There are two points I should like to make, in passing, with regard to the results at

[1] POSTSCRIPT.—Since the date of this Discussion a further search of the literature has revealed a total of 25 cases which have recovered after treatment by sulphanilamide or the red dyes.

Queen Charlotte's Hospital. Firstly, we have obtained no striking evidence of any benefit from these drugs in infections other than those due to hæmolytic streptococci —with the possible exception of staphylococcal infections. This statement should not be understood to include the puerperal infections of the urinary tract by *B. coli*, but only infections of the genital-tract tissues. Secondly, and this is of interest, we have been trying in the past year to compare the results obtained with sulphanilamide (streptocide) with those obtained with red prontosil previously. Results with the former have been satisfactory; the death-rate has been a little, but not very much, higher; fever has subsided in much the same way as with red prontosil, but the fall is not always quite so spectacular. There have been a few very slight cases of parametritis. We feel that although the results have been satisfactory with sulphanilamide, they have not been quite so impressive as those with red prontosil. I do not want to stress this conclusion—possibly further experience will reverse it. Why it should be so I do not know; in animals the opposite is the case. We are publishing our report on the subject (Colebrook, Purdie and others (1937)).

If I may digress for a moment, it is to say that if we are getting nothing more out of prontosil and sulphanilamide, I feel that it is a great gain that we have been pitch-forked into this question of the difficulty of assessing the results of new remedies. In the next few years we shall be deluged with new compounds, and we have to sit down to consider the problem as how to know whether one is 20% or 50% better than the other.

The medical "man in the street's" idea that you can take alternate cases is not good enough. I do not know how it is to be done, but it is a question which needs serious thought. One point I would make is, that our experience at Queen Charlotte's has shown the great value of having units for this purpose such as we have at that hospital—a small hospital with a comparatively large laboratory equipped for attacking the problem from several sides, and staffed with people who have nothing to think about but the one problem. Progress in medicine would be faster if we had more "workshops" as one might call them, of the type we have at that hospital, with plenty of people in the laboratory for working out the several problems, because they do require an enormous amount of work.

I had intended to say something about the action of these substances, but I shall not. I think Dr. Buttle will have something to say as to what little actually is known about this.

Instead, I shall deal with the toxic effects of these drugs, a subject of more practical interest. It seems almost inevitable that new drugs have to go through two phases before we can see them in their true perspective as to toxic effects. The first phase is that in which the toxic effects receive too little emphasis in the medical press: in the second phase they receive too much. With regard to these particular drugs we are in the second stage at present, and medical journals are flooded with reports of one, two, or three cases showing toxic effects, and nothing is said of the hundreds of cases which show no such effects.

I will tell you what our experience has been:—

We have treated 150 cases with sulphanilamide for a period of one to two weeks and about 50 cases for shorter periods, i.e. one or two days. We have treated nearly 70 cases with red prontosil. The most prominent toxic effects we have observed have been cyanosis, although sulphate purgatives have been rigorously avoided. More than 50% of the cases treated with sulphanilamide have shown some degree of cyanosis—in the majority, of slight degree. In the 58 cases we are recording in our paper there was sulphæmoglobin found in 13, methæmoglobin in another 24, the two together in 8 cases. Methæmoglobin has been more prominent. In eight cases showing some cyanosis we could find neither methæmoglobin nor sulphæmoglobin. There were three cases in which the cyanosis was accompanied by an alarming amount of prostration, so severe that the drug had to be discontinued in all three. One of these three was having very large doses. Whether the prostration was

intimately associated with the cyanosis I do not know. All were heavily infected cases; one had general peritonitis and septicæmia. Apart from this incidence of prostration, cyanosis did not appear to us to be a serious matter.

Secondly, in some cases we saw what the Americans have been describing as "drug fever"; this is a type of fever we have seen in 6 or 7 cases out of 100. There would be nothing to suggest from the clinical signs and symptoms that the case was having a recrudescence of the disease, but the temperature rose and we stopped the drug, and on stopping the drug the temperature fell. Long and Bliss (1937) have produced fever by injecting 2·5 grm. of red prontosil, and last winter, in America, I saw two or three patients who got fever every time they had sulphanilamide.

We must therefore accept the fact that some patients will have fever due to the drug. In about 20 cases there has been recurrence of fever a few days after we stopped the drug and this has been attributed to some recrudescence, but in every case on resuming drug treatment fever subsided and convalescence proceeded normally.

Apart from drug fever, which we must call a toxic effect, the chief difficulties have been disturbance of the central nervous system, but nothing serious; there have been at least two cases of mental disturbance with hysterical fits which we have never previously seen, but our psychiatrist was not convinced that any one of them was due to the drug. We should normally expect about two cases in 100 to present mental symptoms. In some of the patients headache has occurred, slight dizziness, visual disturbance, occasionally spots in front of the eyes, slight dimness of vision, paræsthesia and, in one case, diminution of tactile sensibility. In two of the cases there was slight jaundice. We have not seen anæmia, but we have not made routine blood-counts. With one exception no case suggested the development of anæmia. Nor have we detected agranulocytosis. Morbilliform rashes, such as have been associated with fever in America, have not occurred.

Our conclusion about these toxic effects is that we must recognize them, and I think we shall have to conclude that some patients have an idiosyncrasy to this drug. It seems desirable that these drugs should not be sold over the counter, and that they should only be used on medical prescription, and rarely given for more than two weeks. They certainly should not be used as a "shot in the dark" for the treatment of infections in which we have no reason to suppose the drugs would do any good. Nor should they be used casually for obstetric prophylaxis. Their use is justified in certain circumstances in which there is special danger of hæmolytic streptococcus infection.

Our experience—so far as it goes—supports that of the Americans in that we believe that the drugs are better tolerated by patients in bed than by those who are up and about. It is well to keep in mind that all the samples of the drugs on the market may be uniform in composition. This is suggested to me by the varying accounts of toxic effects which are coming in. The Americans have seen morbilliform rashes and we have not; others have not seen cyanosis at all; we have.

Finally, may I remind you that when Ehrlich was here in 1913 he told us we must be prepared to run some risks if we were going to do effective chemotherapy. We should remember the lesson of "606". Since it was realized that "606" might have toxic effects, the manufacturers went to work to produce a substance which was less toxic, in fact which became less and less toxic and less and less curative. Possibly the same will happen in regard to these drugs and we should be on our guard against it.

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Dr. G. A. H. Buttle: As Dr. Colebrook has dealt with the use of these drugs in infections due to hæmolytic streptococci, I shall try to present evidence of their usefulness in other infections. I shall refer to some new compounds and finally, refer to what we know of the mode of action of sulphanilamide.

Non-hæmolytic streptococcus.—In the treatment of non-hæmolytic infections (endocarditis with *S. viridans*) the results have been uniformly negative. Eight strains of these organisms, however, kindly supplied by Dr. Elliot, were almost as susceptible to the drug in broth medium and in blood *in vitro*, as the hæmolytic streptococcus; one, of the *S. fæcalis* type, was not susceptible. It is possible that the lack of therapeutic effect is due to the low phagocytic power of the blood of the patients, or it may be that the streptococci in the heart valves are inaccessible to the drug.

Meningococcus.—In mice the results have been very striking. Mice infected with 1,000,000 fatal doses can be cured with sulphanilamide (compared with 10,000 in the case of mice infected with hæmolytic streptococci). It is not necessary to continue the administration of the drug, as one dose is almost as effective as repeated doses. The results of delaying treatment for two to five hours after infection are not as good, however, as with streptococcal infections (Proom [14]). Since the drug gets into the cerebrospinal fluid in almost as high a concentration as into the blood, good results might be expected in meningococcal meningitis. There is, as yet, very little clinical evidence of its value, but Schwentker *et al.* [16] have published the results of ten cases, nine of which were successfully treated. It seems possible that the treatment may fail if started late in the disease, as large amounts of toxic substance may have already been formed; these are not neutralized by the drug, the only effect of which is on the growth of the cocci. In the one failure reported by Schwentker the fluid was sterile after the treatment.

Gonococcus.—In *in vitro* experiments gonococci are as susceptible to the action of the drug as meningococci. There are, as yet, no experiments published in animals, with the exception of one report by Levaditi and Vaisman [12]. There have been a number of clinical reports (Dees and Colston [5], Crean [4], Von Grütz [17], and Anwyl-Davies [1]). All these authors, except Anwyl-Davies, find that the use of sulphanilamide or its derivatives shortens the period of treatment to about one half of the usual time, but there are a few failures reported by each of the workers. Anwyl Davies finds that sulphanilamide is without effect.

Typhoid coli group.—Figure 1 shows that sulphanilamide cures mice infected with about 100 fatal doses of *B. typhosus*. One dose of the drug gives as good a result as repeated doses (Buttle *et al.* [3]), although the mouse blood contains living *B. typhosus* for very long periods, up to two weeks after the infection. There have been as yet no clinical trials of the drug in this infection.

The second part of figure 1 shows that sulphanilamide has a pronounced effect in Sonne dysentery infections of mice; infections with 10,000 lethal doses can be cured. This suggests that sulphanilamide may be uesful in the control of the infantile diarrhœa which is sometimes due to this organism. We have not yet obtained Shiga or Flexner strains of sufficient virulence to enable us to test the effect of the drug in these infections.

From the clinical standpoint the most striking therapeutic results have been obtained in urinary infections with *B. coli* (Huber [10], Kenny [11], and Helmholtz [9]); the last author also finds that *B. proteus* infections are particularly susceptible. On the other hand, urinary infections with *S. fæcalis* are insusceptible to sulphanilamide, but are readily treated with mandelic acid.

Staphylococcus.—There is, as yet, no clinical evidence published with regard to the treatment of staphylococcal infections in man, but it is possible to cure mice infected intraperitoneally with virulent strains, in suspension with 5% mucin.

Figure 2 shows experiments by Dr. Parish and myself. 80% of the animals infected with 100 lethal doses of a virulent staphylococcus (bovine mastitis) could be

kept alive for forty-eight days, but on post-mortem examination at the end of this time half of these animals were found to contain staphylococcal abscesses; the other half showed no lesions and cultures were sterile. With 10,000 lethal doses there was only a delay in the time of death, and the staphylococcal abscesses were numerous.

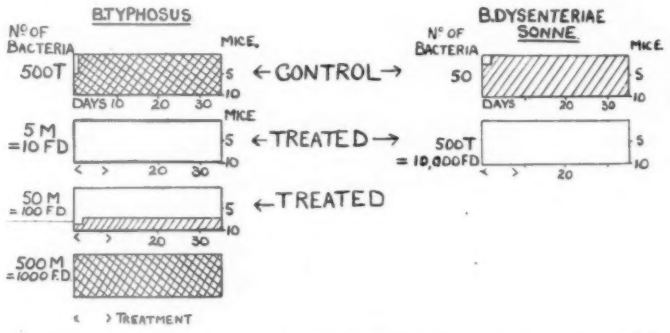

FIG. 1.—Treatment of *B. typhosus* and *B. dysenteriæ* (Sonne) infections in mice with sulphanilamide. Each rectangle represents an experiment with 10 mice, each mouse corresponding to a strip one-tenth of the depth of the rectangle (scale of ordinates—"mice"). The time each mouse survived is indicated by the length of the white area corresponding to each mouse (scale abscissæ—"days"). The shaded areas represent animals that died during the time of observation (thirty days), and the day of death is indicated by the position of the left end of the shaded area. The "therapeutic effect" of the drug is indicated by the extent of the white area in each rectangle.

T = thousand. M = million. F.D. = fatal dose.

Treatment—25 mgm. of sulphanilamide twice daily for seven days (arrow heads).

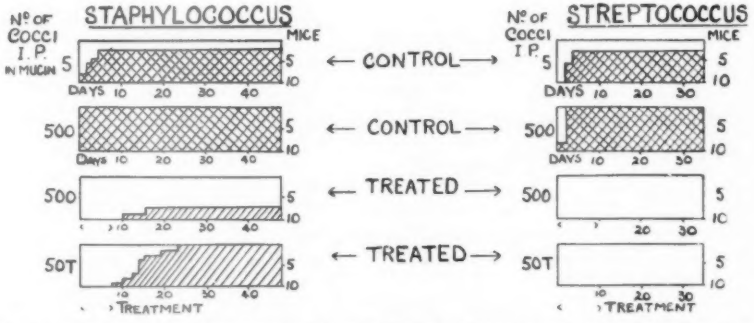

FIG. 2.—Treatment of staphylococcal and streptococcal infections in mice with sulphanilamide. *Dose.*—Staphylococci—25 mgm. of sulphanilamide twice daily for seven days. Streptococci—50 mgm. of sulphanilamide once daily on 1st, 2nd, 3rd, 4th, 6th, 9th, and 12th days.

All animals infected with staphylococci and dying after treatment showed a number of abscesses; of those that survived half showed abscesses on post-mortem examination.

The mice cured of streptococcal infection were free from organisms.

See fig. 1 for further explanation. ΔX5ı ΔX5ı

Figure 2 also shows a comparison between the results of treating staphylococcal and streptococcal infections of approximately equal virulence. The staphylococcal infection was much more difficult to get rid of than the streptococcal, probably owing to the tendency to the formation of local abscesses. From this evidence we should not expect as good clinical results in the treatment of staphylococcal as in streptococcal

infections, although in our mouse experiments with virulent strains sulphanilamide gave better results than antitoxic serum.

Domagk [6] has recently published results with the compound "uliron" $NH_2 \langle\rangle SO_2NH \langle\rangle N(CH_3)_2$. This compound is said to give better results in staphylococcal and gas-gangrene infections than sulphanilamide.

Gas gangrene.—There is one clinical report (Bohlman [2]) of three cases of gas-gangrene infection successfully treated with sulphanilamide ; in one case the recovery was dramatic.

Pneumococcus.—Gross and Cooper [7] have reported that sulphanilamide cures rats infected intranasally with Type III pneumococci. In a preliminary report Heintzelman *et al.* [8] found that the drug was useful clinically.

In infections of mice with pneumococci Types I and II sulphanilamide only delays death (Buttle *et al.* [3]), although there is a great variation in the susceptibility of different strains as indicated by the results of Rosenthal [15].

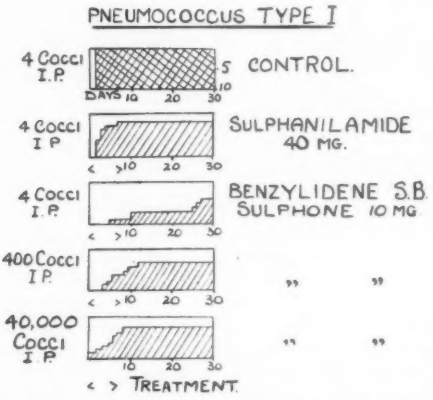

FIG. 3.—Comparison of sulphanilamide and benzylidene Schiff's Base of 4 : 4'diaminodiphenylsulphone—$C_6H_5CH : NC_6H_4SO_2C_6H_4NH_2$—on infections of mice with Pneumococcus Type I.
For further explanations *see* fig. 1.

Figure 3 shows that the benzylidene Schiff's base of 4 : 4'diaminodiphenylsulphone (a compound made by my colleague Mr. Gray) is more effective, although the results are not comparable to those with sulphanilamide in streptococcal infections. This difference between the drugs is probably due to the maintenance of a more constant bactericidal effect in the mouse with the sulphone ; it is possible that the difference would not be so marked in human infections.

The mice which were cured of this infection were immune to a further infection. In similar experiments with streptococci the mice did not become immune. As there is little difference between the susceptibility of the streptococcus and the pneumococcus to sulphanilamide *in vitro* it is possible that the failure in therapeutic experiments with the pneumococcus—delayed death-time instead of complete protection—may depend on the production of more noxious toxic substances by the small number of cocci which remain in the treated animals.

Table I shows that if sulphanilamide is given to mice infected with pneumococcus Type I immediately after infection they can be saved with small amounts of antitoxic serum given eighteen hours afterwards, whereas much larger quantities of serum are ineffective without sulphanilamide. Sulphanilamide given at the same time as the

TABLE I.—TREATMENT OF PNEUMOCOCCUS I INFECTIONS WITH SULPHANILAMIDE AT DIFFERENT TIMES AND SERUM EIGHTEEN HOURS AFIER INFECTION

Serum dose 18 hrs. after culture Brit. Units. i.v.	Mice surviving 12 days		
	Serum only	Sulphanilamide started at time of infection	Sulphanilamide 18 hrs. after infection
250	$^{0}/_{10}$ (2)		$^{0}/_{10}$ (1·5)
25		$^{8}/_{10}$ (10)	
10		$^{6}/_{10}$ (8)	
5		$^{5}/_{10}$ (7·5)	

Figures in brackets = mean survival times.

serum is not more effective than serum alone (experiment by my colleague Miss A. M. Brown). This experiment suggests that sulphanilamide might be useful for early administration to cases in which serum has to be delayed for typing the organism.

New drugs.—4 : 4′diaminodiphenylsulphone is much more effective in streptococcal infections in mice than sulphanilamide ; it has not been used clinically owing to its toxicity. The diacetyl derivative (CH_3CONH ⬡ SO_2 ⬡ $NHOCCH_3$) is, however, only slightly less active than the parent substance in mouse infections, and

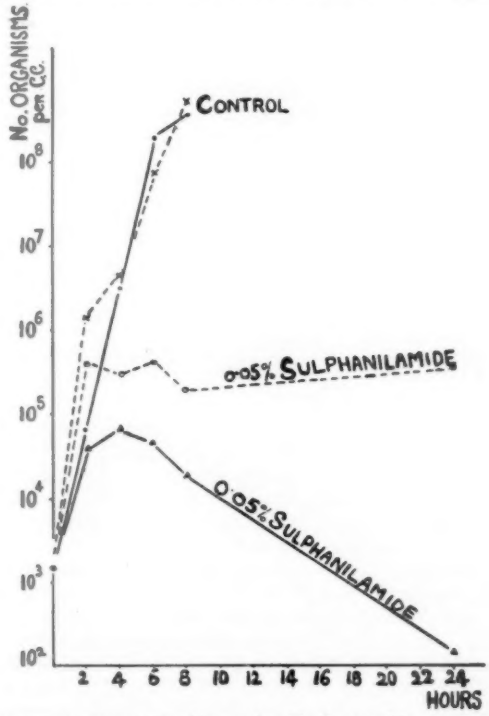

FIG. 4.—The rate of growth of streptococci in monkey blood rotated in closed tubes at 37° C.
Ordinates—No. of organisms per c.c. of blood.
Abscissæ—Time in hours.
The control curves show the rate obtained without sulphanilamide. The dotted lines are for blood from which leucocytes have been removed, and the full lines, normal blood.

it is not at all toxic to mice. Clinical trials now in progress in France indicate that this substance is just as effective in human gonococcal infections as sulphanilamide, whilst it gives less trouble owing to its lower toxicity [13].

Mode of action.—Table II shows that sulphanilamide has only a small effect in

TABLE II.—BACTERICIDAL EFFECT OF SULPHANILAMIDE IN BLOOD.

Blood incubated 48 hrs.	Human	Human without leucocytes	Rabbit
No. of strep. killed by 0·5 c.c. blood	5	0	0
No. of strep. killed by 0·5 c.c. blood + 0·5% sulphanilamide	500,000	50*	50*

* Growth of larger number delayed.

killing streptococci in blood from which the leucocytes have been removed, although it will delay the growth of large numbers. Its principal function appears to be delaying the growth of the cocci, and possibly damaging them in some way which promotes their phagocytosis. The means by which the damage is done is still unknown.

Figure 4 (p. 9) shows the rate of multiplication of 1,200 cocci in blood with and without leucocytes and in similar specimens containing sulphanilamide. The striking feature is that there is no difference in the first two hours of incubation; the action of the drug on the cocci only comes on very slowly. In blood without leucocytes there is no phase of reduction of numbers comparable to that obtained in the presence of leucocytes. (All these experiments were done in 1 c.c. ampoules with tight cotton-wool plugs; the ampoules were rotated once a minute.)

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Dr. M. Mitman: My contribution to this discussion is an account of some simple clinical trials of the benzyl derivative in the practice of a fever hospital. In the infectious diseases the importance of the hæmolytic streptococcus cannot be over-emphasized. Apart from its rôle as the primary ætiological agent in puerperal fever, scarlet fever, and erysipelas, it is responsible, as a secondary organism, for a high percentage of the complications in other infectious diseases. Otitis media, mastoiditis, adenitis, bronchopneumonia, and empyema, in such diseases as measles and whooping-cough, are almost invariably due to hæmolytic streptococci, and those septic complications which occasionally occur in diphtheria and other fevers are frequently due to the same organism. Since these complications are responsible for a considerable amount of the morbidity and mortality in infectious diseases, the appearance of a successful chemotherapeutic agent against the hæmolytic streptococcus promised to be of considerable importance in fever practice. Scarlet fever and erysipelas were the obvious first choice in trying out the new drug.

In scarlet fever the hæmolytic streptococcus produces clinical manifestations which, for convenience, may be divided into toxic and invasive ones. This distinction

is to a certain extent artificial, but it serves at least one useful purpose: it permits the division of the clinical features into those which are readily influenced by serum and those which are not. There is to-day general agreement that scarlatinal antitoxic serum rapidly neutralizes the general and local toxic manifestations such as pyrexia, headache, malaise, vomiting, sore throat, and the rash, and influences the amount and extent of the subsequent desquamation. On the other hand, there is still considerable divergence of opinion as to the value of serum in the prevention and treatment of complications such as otitis media, adenitis, rhinitis, nephritis, arthritis, and septicæmia—all of which are usually attributed to the invasive properties of the streptococcus. When the opening speakers and their collaborators reported their early success with the original prontosil in puerperal septicæmia—in which disease the invasive character of the hæmolytic streptococcus is of paramount importance—it seemed a reasonable inference that the drug might influence the complications of scarlet fever. The investigation I am recording was therefore undertaken with the object of determining if all the clinical manifestations of scarlet fever could be wiped out—the toxic ones by the administration of serum, and the invasive ones by sulphanilamide. There was, however, one obvious objection. Scarlet fever to-day is a relatively mild disease with a trivial fatality rate. When the investigation began in July 1936, reports of the toxic effects of the drug were accumulating, and there was a distinct possibility that the treatment would be more dangerous than the disease. At this time it was represented to me that the benzyl derivative, proseptasine, was less toxic than the prontosil-red then marketed, and I decided to use it instead, even if it should prove to be less active.

The cases of scarlet fever investigated numbered 355, and were divided into three groups. The first was a control group; the second received antiscarlatinal serum; the third received both serum and proseptasine. To eliminate as far as possible other variable factors which are known to influence the result of treatment, e.g. age, season, severity of the attack, nursing and medical attention, the following procedure was adopted:—

Four wards were reserved for the investigation and were placed in the charge of one medical officer—Dr. J. C. Hogarth. In each of the wards patients were allotted to the three groups in strict rotation. Treatment did not begin until the cases had been seen and graded by Dr. Hogarth. This meant that, for uniformity, treatment was not instituted until the morning after admission. All doubtful cases and all cases of surgical scarlet fever were excluded, as were all cases suffering from intercurrent conditions unrelated to scarlet fever and likely to influence the duration of the pyrexia and the stay in hospital. Two cases were excluded from the control series because their original toxæmia was sufficiently severe and prolonged to give rise to some anxiety, and it became a moral obligation to administer serum. This, of course, affected the results in the control group advantageously—particularly as the number of severe cases in the series is small.

After preliminary cautious trials the dosage of proseptasine decided upon was the following:—

Children under 5 years of age were given 0·5 grm. twice daily for three days, followed by 0·5 grm. once daily for four days. On the sixteenth day of the disease a second course of 0·5 grm. daily began, and was continued for seven days.

Children over 5 years of age were given 0·5 grm. three times a day for three days, followed by 0·5 grm. twice a day for four days. The second course from the sixteenth day onwards was 0·5 grm. twice a day for seven days.

The object of the two courses was to cover those periods of the illness in which clinical manifestations commonly occur. The first course was intended for the treatment of the initial symptoms and the early complications, the second for the

prevention and treatment of the later complications which commonly appear in the third week of the disease.

The effect of the treatment was judged from two criteria: the duration of the initial pyrexia, and the incidence of complications. The initial pyrexia was considered to be over when the temperature had remained normal for twenty-four hours or more. This is, of course, an arbitrary standard, but it was applied equally to all three groups. The first day of admission was counted as one day, irrespective of the time of the day the patient was admitted. As the personal element is of some importance in determining the presence of complications, the decision in every case was left to one observer—(Dr. Hogarth).

The results were disappointing (*see* Dr. Hogarth's tables of the chief findings, p. 17). No significant difference was observed in the duration of the initial pyrexia or in the appearance of the complications. The tables do show some differences, but the original aim was to eliminate complications, and in this respect the experiment was a failure. I will leave the discussion on this until I have described the results in erysipelas.

Whilst the work on scarlet fever was proceeding, proseptasine was tried in various other conditions, including erysipelas, and the results were promising.

From January 1 to October 1, 1937, 59 cases of erysipelas were treated with proseptasine. The age-distribution is given in Table I. The ages of the patients

EASTERN HOSPITAL, JANUARY 1 TO OCTOBER 1, 1937.

Proseptasine in Erysipelas.

TABLE I.—AGE-DISTRIBUTION OF 59 PATIENTS.

Age	Under 10	10–	20–	30–	40–	50–	60–	70–	80+
Number of patients	5	7	9	4	8	8	12	5	1
	(3)	(0)	(1)	(2)	(3)	(5)	(5)	(2)	(0)

varied between 2 and 83 years. (The figures in brackets are the number of males. The differences in numbers between the sexes was due to greater amount of ward accommodation for females.) Five cases had had previous attacks of erysipelas. One had had six previous attacks, another three, and a third two.

The anatomical distribution of the lesions is given in Table II. The dose of

EASTERN HOSPITAL, JANUARY 1 TO OCTOBER 1, 1937.

Proseptasine in Erysipelas.

TABLE II.—ANATOMICAL DISTRIBUTION OF LESIONS.

Face	50
Lower extremity	7
Face and lower extremity	1
Upper extremity	1
Total	59

proseptasine employed was 1 to 1·5 grm. three or four times a day. At the beginning this was continued daily for as short a time as three days in those who responded rapidly, but later, when experience had shown that relapses occurred readily, the treatment was continued for seven or more days. Two patients had received anti-streptococcus serum before admission.

Sulphanilamide or related substances have by now been widely used in erysipelas, and all the results reported have been favourable. The largest recorded group

treated with the benzyl derivative was that of Bloch-Michel, Conte, and Durel, which consisted of 180 cases. My results are in close agreement with theirs.

Although mine was not a controlled series, previous experience of serious cases of erysipelas warrant me to say with certainty that the results were excellent. Among the 59 cases there were 9, mostly elderly patients, who were seriously ill, but there were no deaths. The fatality rate of erysipelas of the extremities is usually given as 20%. There were 9 such cases in this series and all recovered. To me, the most striking feature of treatment with proseptasine is that, since its introduction, patients with the disease have ceased to give me any serious anxiety.

The first effect, usually observable within twenty-four hours, is a cessation of spread of the patch. Indeed, if this does not occur I take it as an indication to increase the dose. There is a rapid improvement in the toxic symptoms; the temperature usually falls to normal in twenty-four to forty-eight hours, and the erythematous plaque fades in three or four days. The duration of stay in hospital is, in consequence, considerably diminished, most patients being fit to go home in about a fortnight. As an example, I will quote the case of a woman aged 72 with erysipelas of the nose and leg. The condition was complicated by the presence of senile myocarditis and bronchitis. She was seriously ill on admission and was given 1 grm. of proseptasine three times a day. She was fit and discharged from hospital in nine days.

In Table III the frequency distribution of the duration of stay in hospital is given. The high percentage of cases discharged within a fortnight can readily be seen.

EASTERN HOSPITAL, JANUARY 1 TO OCTOBER 1, 1937.

Proseptasine in Erysipelas.

TABLE III.—FREQUENCY DISTRIBUTION OF STAY IN HOSPITAL.

Days	Less than 7	7–	14–	21–	28–	35+	Total
Number of patients	2	29	14	6	3	5	59

Minimum stay	... ...	6 days
Maximum stay	(uncomplicated)	38 ,,
,, ,,	(pernicious anæmia)	105 ,,

One point which requires emphasis is the liability of the disease to relapse after the cessation of treatment. In this series four cases relapsed, one of them on two occasions. In two patients the relapses occurred in hospital. The first was a woman aged 57 who had a moderate attack of facial erysipelas and was treated with 3 grm. a day. In three days the temperature was normal, the patch had disappeared, and treatment was stopped. Three days later a relapse occurred and the eruption reappeared, but after two days of further treatment it cleared up. The second was a man who received 4·5 grm. a day for ten days. The relapse appeared ten days after the proseptasine was stopped, and responded readily to further treatment. In the literature recurrences are recorded in both animals and man. Long and Bliss report that in mice there may be relapses as long as sixty days after the cessation of treatment. It is therefore necessary to persevere with the drug for several days after the symptoms subside.

Now I want to consider the reasons for the failure of the drug in scarlet fever. In view of the success in erysipelas, I think one can exclude inactivity of the drug and inadequate dosage as possible causes, although I am now of the opinion that the first course of treatment should have been longer—say, ten days. Another possibility is that the standards by which the effects were judged, namely the duration of the initial pyrexia and the frequency of complications, were inadequate for a proper

assessment of the results. There is, I think, some substance in this objection, but there can be no doubt that the drug failed to eliminate complications, and this was the original object of the experiment. Peters and Havard report a controlled series of cases of scarlet fever treated with proseptasine. It is true that they found a significant difference in the number of cases which developed complications, but the sum of the individual complications was almost identical in the test and control groups. We are left, then, with the probability that the hæmolytic streptococci responsible for scarlet fever are relatively more resistant to the drug than other pathogenic hæmolytic streptococci. The reports of Colebrook and Kenny, Long and Bliss, and Finklestone-Sayliss, Paine and Patrick all indicate that the action of sulphanilamide varies, not only with the group, type, and strain, but even with the age or phase of a particular strain. Poor effects are recorded upon hæmolytic streptococci of low-mouse virulence. It is therefore not unreasonable to suggest that the strain, or strains, responsible for the mild scarlet fever now prevalent, are either unaffected or little influenced by proseptasine.

Singularly few toxic effects of the drug were observed. No routine examinations of the blood were made, but there were no cases with gross clinical evidence of damage to the blood or blood-forming organs. No cyanosis was seen, and even the mild toxic symptoms were rare. The chief toxic manifestation was a rash, which occurred in five cases. Cutaneous manifestations of various kinds have been reported by Menville and Archinard, Goodman and Levy, Frank, Schonberg, Newman and Sharlet, and others, but the account which most closely agrees with the type of eruption seen in this series was that of Schwentker and Gelman. The rashes, which usually come on ten to fourteen days after treatment began, were maculo-papular ones, most closely resembling rubella at the beginning, but later becoming more morbilliform. In distribution they were usually, but not invariably, generalized. They were not limited to, or more profuse on, the parts exposed to sunlight. General disturbance and pyrexia were trivial, and the condition cleared up in about three days.

I therefore came to the conclusion that the claim made that the drug was of low toxicity was justified. I am not in a position to express an opinion on the relative efficiency of the benzyl derivative as compared with sulphanilamide. Whitby decided, from experimental evidence, that the benzyl and phenyl-propyl compounds were as effective and less toxic than sulphanilamide. My experience does permit me to say that proseptasine is easy to give, is of low toxicity, is strikingly successful in erysipelas and relatively ineffectual in scarlet fever.

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Mr. G. Discombe (*Abstract*): Among about 200 cases treated with sulphanilamide at St. Bartholomew's Hospital, no serious complications attributable to the drug have been observed. Numerous cases of cyanosis attributable to methæmoglobinæmia

have been seen but none have shown any signs of oxygen lack. Sulphæmoglobinæmia has not occurred in any patient since laxatives were forbidden and low residue diets and liquid paraffin prescribed as a routine for all patients treated with the drug. Cyanosis in absence of abnormal pigments in the blood occurs in some patients, but is important only in the immediate post-operative period, when it is frequently due to pneumonia.

Professor Arthur Green said that Ehrlich's comparison of dyestuffs and drugs was rather more than an analogy.

A dyestuff must not only possess colour but must have an affinity for the substance to be dyed. Similarly, for a drug to be active it must possess a degree of toxicity and an affinity for the cell constituents.

Further, there were dyestuffs which had a differential effect, and the ideal remedy in medicine would be a substance which had an affinity for the cell constituents of the invading organism, but none for that of the host. While this ideal might never be wholly realized there were drugs nowadays which possessed a very much greater affinity for the cell constituents of the microbes than for those of the host. All the substances mentioned in the discussion were derivatives of aniline; P-aminobenzene sulphonamide (prontosil album) might be correctly termed aniline sulphonamide. Aniline itself was highly toxic and probably had a strong affinity for all cell constituents and so could not be used.

If one put into the molecule of aniline a sulphonic acid group, thus obtaining sulphanilic acid, one entirely changed the properties. Practically all toxicity and affinity were lost, but if one went half-way and introduced the slightly acid sulphonamide group instead of the strongly acid sulphonic group, the effect to be anticipated would be as seen in the drugs under discussion.

The sulphonamide group appeared to be one which held just the right degree of acidity and solubility so that the product would show a differential attraction between the cell constituents of the microbe and the host. On some such lines as this an explanation of the therapeutic action of these compounds would probably be found.

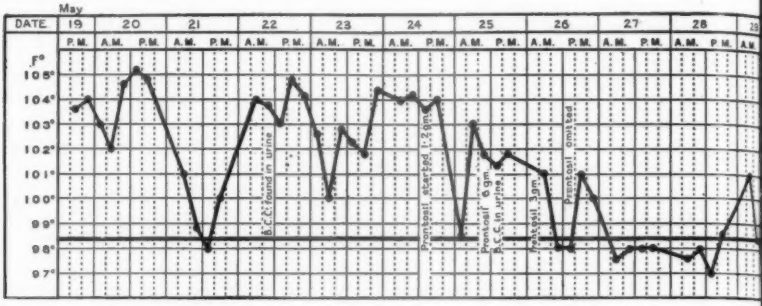
Dr. E. P. Poulton said that when he began using these substances, Dr. E. H. Koerner, at Guy's Hospital had mastered E. W. Todd's technique of antistreptolysin titration, and it was felt that the opportunity had arisen for treating various "occult" hæmolytic streptococcal infections with P-aminophenyl sulphonamide.[1] "Occult" hæmolytic streptococcal infections were those in which the actual causative organism could not readily be identified.

A high antistreptolysin (A.S.L.) titre in the serum was taken by Dr. Poulton and his colleagues as evidence of occult infection and as an indication for specific treatment. He did not want his hearers to think that high A.S.L. titres were invariably present in hæmolytic streptococcal diseases, because in severe hæmolytic streptococcal septicæmia one could get low titres. In obvious streptococcal infections with streptococci in the blood, which had been successfully treated, there might be values up to 2,000 A.S.L. units. In one case of very severe exfoliative dermatitis, streptococci were present in the blood, and the titre was only 50 (normal). P-aminophenyl sulphonamide was given, and he was at first pleased with the result. Later, however, the patient died and a small abscess in the lung was found, and pus was present in the sinuses. On the other hand, there was a case of erysipelas in a diabetic patient with a large amount of serous exudation over the patches of erysipelas, in which the A.S.L. titre was 33, and yet the patient did extremely well on P-aminophenyl sulphonamide. In six days the titre had risen to 71, a rise suggestive of streptococcal infection, even though the titre was within normal limits.

[1] NOTE.—P-aminaphenyl sulphonamide = sulphanilamide.

The cases he would group under occult hæmolytic streptococcal infection were :—

Acute rheumatism. He had two resistant cases which seemed to do well with these substances, and there was a small girl with purpura who gave a high



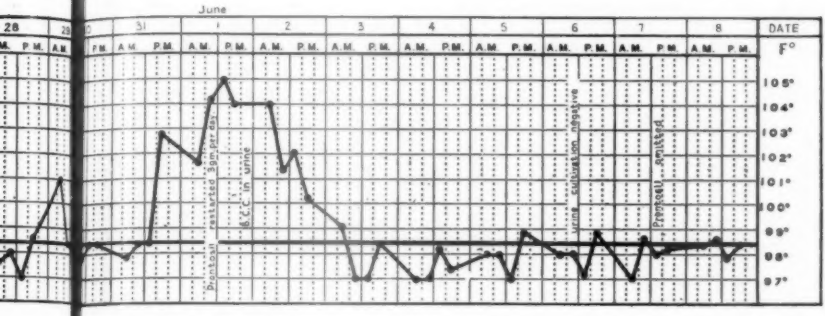
A.S.L. titre ; this case cleared up very quickly with P-aminophenyl sulphonamide. He divided the cases of rheumatoid arthritis with high titres into (*a*) acute febrile, (*b*) chronic febrile, and (*c*) chronic afebrile, often with occasional spikes of temperature up to 99° and 100° F.

There were three acute cases, and all did well, though it was difficult to know whether the effect was produced by the treatment. The temperature fell gradually and there had been a previous period when nothing seemed to have any effect. In Group (*b*) one woman had fever eighteen months, and during the P-aminophenyl sulphonamide treatment the temperature was lower than at any other time ; two other patients did well, and in two there was no striking improvement. After the P-aminophenyl sulphonamide was stopped, the temperature rose again. In chronic afebrile cases (*c*) the results were uncertain though the remedy might be tried.

A point of importance was that there were cases of hæmolytic streptococcal infection apparently associated with other diseases—an unexpected occurrence. The patient to whose case he would refer in this connexion had abdominal actinomycosis, and ran a continuous fever for a considerable period. Deep X-rays were tolerated badly, and only small amounts of iodine could be taken. Therefore it was eventually decided to try his antistreptolysin titration ; this was high. The effect of sulphanilamide was that the temperature came down in five days. The patient put on weight, was discharged to Carshalton in September, and has had no temperature since.

The temperature chart shown above is that of a girl aged 7 who previously had had bad health, with otitis media and attacks of rheumatism ; she also had recently suffered from attacks of sore throat, accompanied by diarrhœa and vomiting. On admission, with high fever, she was at first considered to have *B. coli communis* pyelitis, as that organism was recovered from the urine, but there were no kidney symptoms. On the sixth day after admission the A.S.L. titration was 140, perhaps just above normal, and 1·2 grm. of P-aminophenyl sulphonamide were given that day and 6 grm. the next. A remarkable fall of temperature followed. On the tenth day the A.S.L. titre had risen to 280. When the drug was omitted the temperature again became high. The patient had been very ill, and two house physicians detected at one time a pericardial rub for quite a short period. It is

suggested that in spite of the coli bacilluria, which also cleared up under P-amino-phenyl sulphonamide, the temperature was really due to occult hæmolytic streptococcal infection.



Dr. J. C. Hogarth said that his tables gave details of the series of 355 cases of scarlet fever referred to by Dr. Mitman.

Table I showed the distribution of cases in degree of severity in each group. It

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TABLE I.—DISTRIBUTION ACCORDING TO SEVERITY IN 355 CASES.

	I Control		II Serum		III Serum and proseptasine	
	No.	%	No.	%	No.	%
Mild	56	48·7	41	32·5	35	30·7
Mild-Moderate ...	21	18·2	19	15·1	18	15·8
Moderate ..	37	32·2	62	49·2	56	49·1
Moderate-Severe	1	0·9	4	3·2	5	4·4
Severe	—	—	—	—	—	—
Total ..	115	100·0	126	100·0	114	100·0

would be seen that there appeared to be a natural selection in favour of Group I in the types classified as "mild", "mild-moderate", and "moderate", but he did not think this was altogether true. Division into these three types was made in an effort to show a more accurate distribution. This was not successful because the cases in these groups were all very mild with consequent difficulty in classification. He suggested that it would be better to take the three types together under the term "mild-moderate". When that was done little difference would be seen between the three groups. The remaining types of case were more easily defined and could be left as they stood. It was from Group I in the type "mild-moderate" that two cases were removed. These cases proved to be so toxic that there could be no justification for withholding serum.

Table II showed firstly the mean day of disease on admission in each group. This

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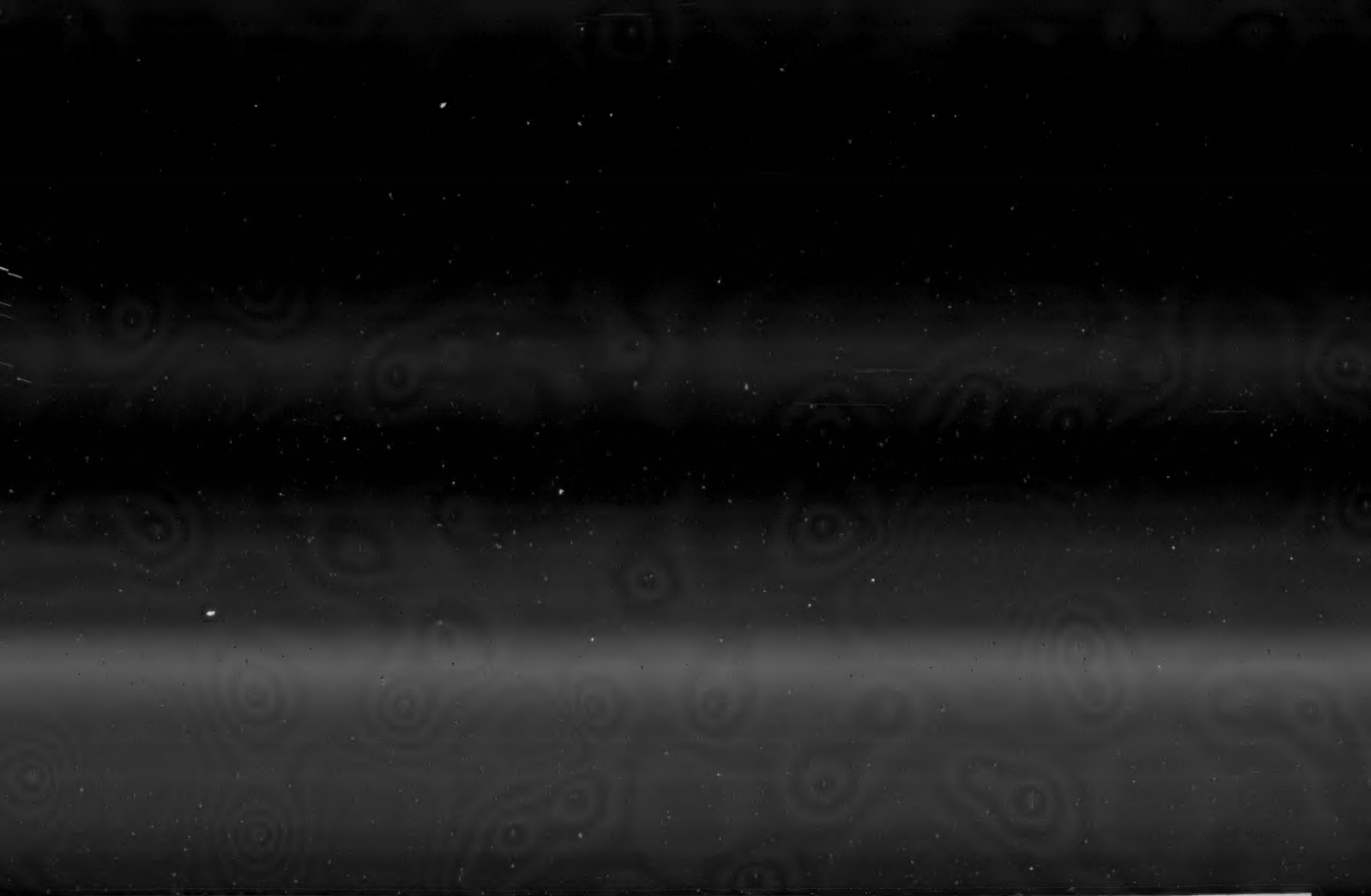
TABLE II.—PYREXIA AND COMPLICATIONS IN 355 CASES.

	I Control	II Serum	III Serum and proseptasine
Mean day of disease on admission	2·4	2·3	2·4
Mean duration in days of initial pyrexia after admission	3·7	3·9	3·9
Percentage of cases with complications	27	23	22

was constant throughout. The second point shown was the mean duration of the initial pyrexia. This again was constant and showed no advantage in favour of either of the three groups. This might give a false impression of the effect of the administration of serum on the initial pyrexia. The temperature in the average untreated case gave a slow curve reaching normal on the day shown, while in the serum-treated groups the average temperature fell, in twelve to twenty-four hours after administration of serum, to within a few points of the normal line, reaching that line on the day shown. The effect of serum on the toxæmia was well marked. Lastly the table showed the complication rate in each group. Although there was an apparent difference in favour of Groups II and III, a statistician to whom the figures had been submitted, had found that the difference was not significant. He (the speaker) hesitated to express an opinion, but his feeling was that the main factor in the production of this result lay in the hæmolytic streptococcus itself.